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HEALTHY AGING AND NUTRITION: THE SCIENCE OF LIVING LONGER

FIELD HEARING

BEFORE THE

SPECIAL COMMITTEE ON AGING UNITED STATES SENATE

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

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HEALTHY AGING & NUTRITION: THE SCIENCE OF LIVING LONGER

THURSDAY, AUGUST 15, 2002

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Baton Rouge, LA

The committee met, pursuant to notice, at 10 a.m., at the Pennington Biomedical Center, Administration Building Auditorium, Baton Rouge, LA, Honorable John Breaux (chairman of the committee) presiding.

OPENING STATEMENT OF SENATOR JOHN BREAUX, CHAIRMAN

The CHAIRMAN. Our Senate Aging Committee will please come to order, and good morning everyone. Thank you all for being with us and in attendance. We want to thank everyone at the Pennington Center for their cooperation in helping us with this Senate Aging Committee hearing today here at the Pennington Center, and thank all of our good friends at LSU for their good, strong support, and we certainly appreciate your allowing us to be here and with your colleagues at the university as well. We are very delighted.

I serve as Chairman of the Senate Aging Committee in Washington, and this hearing really is to allow some of our witnesses to talk about some of the good things that are happening in the area of aging and also to talk about some of the research that is going on and will continue to be going on in this particular area. I want to particularly thank two of our guests who have traveled from Washington and also New York to be with us today. Dr. Pamela Starke-Reed who is with the National Institutes of Health, thank you very much for being with us, and my good friend, Dr. Robert Butler, who has worked with our Aging Committee in so many areas. He is President and CEO of the International Longevity Center in New York City. We thank both of them for traveling to be with us.

Today's hearing I would point out is not science fiction. Our distinguished guests will be discussing some of the current, cutting-edge research which ultimately may add a significant number of years to the human life span. While this topic is indeed very interesting, it's also very exciting, it should be stated also that the increase in life span that we all hope for in long term is not quite yet available. Last September our Special Committee on Aging held investigative hearings to expose fraudulent health care claims being made by people who are nothing more than con men who are trying to sell dietary supplements which they would offer as the

key to longevity. Claims that diseases can be cured and the aging process stopped in its tracks by simply taking a little pill have always been well received by people who are looking for that type of cure. Fortunately as we know, when something sounds too good to be true, it generally is too good to be true and is probably false. As of today there is still no scientific evidence that simply dietary supplements alone will slow the aging process or increase longevity. However, we can keep our fingers crossed and we can hope that the work being done by Dr. Butler, at the National Institutes of Health and the Pennington Biomedical Research Center will be very helpful and very useful and produce results in the near future.

The Pennington Biomedical Research Center was recently recognized by the NIH as an outstanding research center by being awarded over $12 million in grant funds to study the possible benefits of long-term reduction of calories on aging. For many years now, scientists have known that animals on a high-quality, nutrient-rich, low calorie diet live significantly longer and healthier lives. This phenomenon has been demonstrated in worms, monkeys and just about everything in between. Pennington has been chosen along with two other outstanding research institutions to determine if this effect will occur in humans as well. During the next 2 years, human subjects will be placed on a calorie restricted diet and their risk of heart disease, hypertension, diabetes and other medical problems will be closely monitored.

Now, I know many in our audience here in Louisiana must be thinking how are people in Louisiana going to go on a low-calorie diet with all of the temptations that we have in our area. It is not very likely most would think. However, if the diet research proves to have the same beneficial effects in humans that it does in animals, additional research will be conducted to determine how this works at the molecular level. Here is where we start hoping for that miracle pill again. If researchers can determine how caloric restriction works, it is possible that they would be able to duplicate it synthetically. Remember, however, that this is not a reality yet. If by the end of the year you see a supplement claiming that it contains all the herbs necessary to duplicate caloric restrictions, run the other way. It is probably not true.

I look forward to learning more about this incredibly interesting topic from our panelists, and again I want to thank the Pennington Biomedical Research Center and all of the associates at the university for cooperating in this effort. I truly believe that the Pennington Biomedical Research Center can be one of the world's leading institutions in this effort. As Chairman of the Senate Aging Committee, I want to do everything in my power to see that that wish becomes a reality.

The panel of witnesses, as I mentioned, that we have here today are truly distinguished experts that I am very excited to hear from. Their testimony will be made part of our Congressional Record. First we want to hear from Dr. William Patrick. Dr. Patrick will discuss how nutrition and physical activity has positively impacted his life as he has grown older. He is still an active research scientist and is currently the No. 2 ranked tennis player in the State in his age group and was a member of the silver medal winning basketball team at the most recent senior games. He is a person

who I have a great deal of admiration for. My goal in life is to win the national 100 and over tennis championship by being the only entry. [Laughter.]

But perhaps if research proves effective, there will be many more entrants at that time. So first we will hear from Dr. Patrick.

Dr. Patrick, we are glad to have you with us.

STATEMENT OF WILLIAM H. PATRICK, JR., PH.D., BOYD PROFESSOR OF OCEANOGRAPHY AND COASTAL SCIENCES, WETLAND BIOGEOCHEMISTRY INSTITUTE, LOUISIANA STATE UNIVERSITY, BATON ROUGE, LA

Dr. PATRICK. Thank you, Senator Breaux, ladies and gentleman. I am a Boyd Professor of Oceanography and Coastal Sciences here at Louisiana State University. I have been asked by the Pennington Center to discuss some of the aspects of healthy aging from a layman's point of view. I am not a professional in this area, and so I am sort of here as a guest. I was probably asked to speak to this committee because I am the senior active member of the whole LSU system in terms of years of service. There is no one left in the system who was here when I was appointed an assistant professor on July 1, 1953. Although my wife, Ruth, over here does not like for me to tell my age, I am 76 years old, so I have established longevity credentials here. Another possible reason I was asked to speak to you is because I am still carrying on a full program of scientific research and teaching.

I plan to use my time today to discuss what I think are some of the important aspects of healthy aging, and try to illustrate them with my own experience.

Of course, one of the most important requirements for healthy aging is to have good genes. A MacArthur Foundation study showed that about one third of the aging process is controlled by genetics. I was fortunate to have chosen good parents. This leaves two thirds of the aging process due to other factors, all of which are under the control of the individual. These other factors that contribute to healthy aging, according to the MacArthur Foundation report, are good nutrition, regular exercise, stimulating mental activities, and a sense of community.

Good nutrition is an ever-present concern in my family since I have been married for a long time to Dr. Ruth Patrick, a specialist in human nutrition and the recently retired Chief of the Pennington Nutrition Education Program. Of course, I do not faithfully follow good nutrition practices all the time, but I am certainly aware of it when I do not. In addition to a good balance of nutrients in the diet, effective weight control is also important, and although I owe my adequate weight largely to my genetic makeup, I once had to limit my food intake to bring my weight down to a favorable level.

There is no doubt that regular exercise contributes greatly to both the physical and mental aspects of healthy aging. Early in my scientific career I used extensive field work to supplement sports to maintain a healthy body, and I still do considerable field work in many parts of the world as the attached photographs taken from a coastal swamp last July shows. I do not know if you can—if you had it close up, you could see the sweat and mud on this photo-

graph here. This appeared in a German scientific publication as part of a cooperative project with a German research institute. In recent decades, I have still supplemented field work with sports to maintain body vigor. As the Senator mentioned, I play singles tennis and last year was No. 2 in the State Senior Olympics in my age bracket. This year I was one year older and new people were coming in, so I fell to three, but I do not know where I will be next year. I also play basketball, and because I have some good teammates, last year our team won our age bracket's National Senior Olympics silver medal.

Responding to medical needs is an absolutely essential part of healthy aging, and we all appreciate Senator Breaux's efforts in this direction. Taking advantage of the high-quality medical support available in this country will add both time and quality to an aging person's life. My life would certainly not have its current quality without the benefits of hernia surgery, cataract surgery, retina reattachment, arthroscopic knee surgery, dental implants and small doses of blood pressure-lowering and cholesterol-lowering medications.

Engaging in mentally stimulating activities is probably the most important component of my quest for healthy aging. All of us who want to extend their careers beyond ages 65 or 70 owe a debt of gratitude to one of Senator Breaux's earlier colleagues, Claude Pepper of Florida, who championed legislation that eliminated a mandatory retirement age. Even at this stage of my career at age 76, I am the principal investigator of five outside-funded research projects, ranging from basic scientific environmental chemistry studies supported by the National Science Foundation to applied studies of the effect of sea level rise on coastal Louisiana ecosystems. This fall I will be teaching a new course that I developed on the effect of global climate change on the stability of coastal wetlands. Over a quarter century ago I established the Wetland Biogeochemistry Institute at LSU where my colleagues and I are largely funded by grant and contract funds and which has produced over 600 scientific papers and reports covering work done largely in Louisiana but also in many other states and quite a few foreign countries. I still have the same enthusiasm for research that I did a half century ago. In fact, there have been two periods when I felt under considerable pressure to succeed, the first when I started out and was trying to establish myself as a research scientist, and now when I feel the pressure to justify my staying on beyond the normal retirement age.

The MacArthur study found that a sense of community or belonging is important in maintaining a healthy outlook into old age. An active person is involved in a number of communities, and my interaction with several communities brings a great deal of satisfaction. Without doubt the most important is my family consisting of my wife, four children and their spouses and twelve grandchildren. To celebrate her recent retirement, my wife sponsored all 22 of us for a week at Vail, CO, this summer, which did catch me up considerably with community involvement.

In conclusion, I would like to reiterate that the recipe for healthy aging is to build onto a favorable genetic heritage with good nutri-

tion, effective exercise, good medical care, stimulating mental activities, and a sense of community. Thank you.

[The prepared statement of Mr. Patrick follows:]

Testimony to the Senate Special Committee on Aging
Pennington Biomedical Research Center
August 15, 2002

My name is William Patrick. I am Boyd Professor of Oceanography and Coastal Sciences at Louisiana State University.

I have been asked by the Pennington Center to discuss some of the aspects of healthy aging from a layman's point of view. I was probably asked to speak to your committee because I am the senior active member of the whole LSU system in terms of years of service. There is no one left in the system who was here when I was appointed an assistant professor July 1, 1953. Although my wife doesn't like for me to tell my age, I am 76 years old. Another probable reason I was asked to speak to you is because I am still carrying on a full program of scientific research and teaching.

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In conclusion, I would like to reiterate that the recipe for healthy aging is to build onto a favorable genetic heritage with good nutrition, effective exercise, good medical maintenance, stimulating mental activities, and a sense of belonging.

The CHAIRMAN. Thank you very much, Dr. Patrick. That was well stated, and we are delighted to have that in the record. Next we are going to hear, as I indicated earlier, from Dr. Robert Butler who is the President and Chief Executive Officer of the International Longevity Center in the USA, and he is a very special friend of the Special Committee on Aging.

Dr. Butler, glad to have you.

STATEMENT OF ROBERT N. BUTLER, M.D., PRESIDENT AND CHIEF EXECUTIVE OFFICER, INTERNATIONAL LONGEVITY CENTER-USA, NEW YORK, NY

Dr. BUTLER. Thank you very much, Senator Breaux. It is a privilege to be here in Louisiana and to say good morning to everyone, and thank you for this opportunity to speak to the science associated with healthy aging and nutrition. In the last century, as you know, we gained an extraordinary 30 additional years of life, and not only added life but fortunately increased quality of life. There were declining disability rates. My new friend on my right I think is a wonderful illustration of that.

I would like to submit for the record my comprehensive statement but to speak just briefly from it and to say that the International Longevity Center in New York—we do have centers also in Paris, London, Tokyo and Santo Domingo—is interested in helping individuals and societies prepare for this extraordinary increase in longevity and population aging but to do so in positive and productive ways. Therefore, we do focus upon healthy and productive aging. We are particularly interested in maintaining and extending and promoting good health habits, advancing biomedical research and in combating unsubstantiated claims with respect to so-called anti-aging medicine.

I was much impressed to see the Pennington Biomedical Research Center receive such a wonderful grant in support for its studies of nutrition and aging, and that contrasts in my mind so much from the claims unsubstantiated by the anti-aging industry which can be so misleading because it is not based upon scientific validation and well-established measurements. This does become serious from my earlier experience in establishing the National Institute on Aging, we found that some of those who made such unsubstantiated claims actually reduced the amount of support that Congress in its wisdom wanted to give us because Members thought an awful lot of it was foolishness.

Now, the concept of caloric restriction goes back 70 years to a remarkable Cornell scientist named Clive McKay who gave undernutrition, not malnutrition, to rodents and found that by reducing their intake by some 30 percent he was able to extend their lives by about 30 percent. There have been now many studies on many different species to demonstrate this. Since the 1980's the National Institute on Aging has been supporting studies within the laboratories of NIH in Poolseville, MD, and at the University of Wisconsin-Madison on squirrel and rhesus monkeys, and the results at the moment suggest that the animals appear to be younger and that certain biological findings seem to be distinctive, lower blood levels of insulin, lower body temperature and the slower decline of

a particular hormone called dehydroepiandrosterone, or DHEA for short.

Now, it does not seem possible, as already suggested this morning, especially with the wonderful cuisine in this great State, that people will reduce their caloric intake by 30 or 40 percent. But as already mentioned, if we can secure the underlying mechanism, why it is that caloric restriction has its effect, we might be able to create mimetics, that means agents that would mimick the effects of caloric restriction, you will be hearing some of the work being done here and also some of the work of Susan Roberts at Tufts University that will give us further understanding of the underlying mechanism of caloric restriction. Now, it is very important to carry out the best of science as I have described, and I think a very good example of that was the recent, surprising perhaps and certainly in many ways painful findings of the Women's Health Initiative at the National Institutes of Health. For a long time we had depended upon the Boston Nurses Study for information related to the appropriateness of hormone replacement therapy. In retrospect it appears that the health habits of the nurses in that study helped contribute to a misunderstanding and over hopefulness with respect to the concept that hormone replacement therapy would be preventative of heart disease. Having definitive randomized clinical trials and the best scientific methodology has unfortunately demonstrated that such hormone replacement therapy not only does not reduce heart disease but may even be a risk.

Similar things have happened that have led to the evolution of so-called anti-aging medicine. A very respectable scientist, Daniel Rudman, at the University of Wisconsin-Milwaukee, for example, after only a 6-month study found results or increasing muscle mass, decreasing fat and greater elasticity of the skin using human growth hormone. So it is not unreasonable to think this worthy of investigation, and indeed it is. But unfortunately such investigations have not yet been completed, and yet this hormone is being widely touted and used in so-called anti-aging medicine.

Now, just a matter of weeks ago a study appeared in The Lancet magazine by Swerdlow and others identifying individuals who had been treated with human growth hormone between 1959 and 1985 for "dwarfism" and finding that they had an increased incidence of overall cancer mortality and a greater incidence specifically of colorectal cancer and of Hodgkins disease. A warning sign, I think. It is not definitive yet. The point is that we have to undertake critical studies when it comes to dietary supplements, hormones, herbals or any other putative agent said to reduce, reverse or stop aging. We do not have such information at this time.

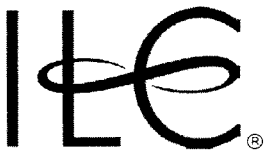
Now, some of it has been deeply wedded to the development of geriatric medicine; that is, the proper, humane, effective, holistic care of older persons. So it is distressing to me to see the term "anti-aging" medicine because aging in many respects can be viewed as a normative process, and we need to differentiate age-related diseases which are the proper purview of those of us who are deeply interested in developing full scale better treatment of older people.

In closing let me also tell you briefly about certain workshops which we hold, modified NIH-type consensus workshops. We bring

together some of the finest scientists in the country to address a particularly critical topic, and we put them to work for 4 days. We ask them to meet the four following charges: What do we really know about this particular topic such as anti-aging medicine? Where we do not know, what is the research agenda that should be developed to help us answer the unanswered questions? Third, what can we responsibly tell the public? Finally, are there implications of a policy character for business, government or foundations? So I would like to present to you, Senator Breaux, some of the workshop results, one on the biomarkers of aging which are means we do not yet possess to accurately evaluate alleged anti-aging agents, one on maintaining healthy lifestyles and a few others which I think would be of use to the country. We do make them available on our own website, and they are also available in print versions.

Let me conclude by saying it is an honor and pleasure to be here, and I hope that the kind of research being done by Pennington and by others supported by the great National Institutes of Health can help us to lead an increasing high quality as well as a longer life. Thank you very much.

[The prepared statement of Dr. Butler follows:]



Written Testimony of

Robert N. Butler, M.D.
President and CEO, International Longevity Center – USA
60 East 86th Street
New York, NY 10028

and
Professor of Geriatrics, Mount Sinai School of Medicine

Before the Senate Special Committee on Aging

United States Senate

Baton Rouge, Louisiana
August 15th 2002

Thank you Senator Breaux for this opportunity to appear before the Senate Special Committee on Aging to discuss the science and research associated with healthy aging and nutrition. My organization, the International Longevity Center, is very interested in this issue. Our mission is to help individuals and societies address longevity and population aging in positive and productive ways, with a specific focus on promoting healthy and productive aging. Our interest in healthy aging extends to the promotion of good health habits across the lifespan, support for biomedical research on aging, and combating the unsubstantiated claims of the so-called anti-aging medicine industry.

I am extremely impressed by the fact that the NIH has provided a substantial grant to the Pennington Biomedical Research Center to study nutrition and aging, which are so important both to quality of life and length of life. Moreover, such serious longevity research provides a clear contrast to the claims of the so-called anti-aging medicine industry. It is important to emphasize that no specific compound or treatment, natural or artificial, has yet to be proven to slow aging in people. Any advertisement or promotion of an "anti-aging" product is therefore misleading, not based on any valid scientific evidence, and possibly dangerous. I'd also like to clarify that anti-aging medicine, despite its claims, is not an established specialty - it has not been recognized as such by academic or organized medicine.

Unfortunately, the claims of anti-aging marketers distract from legitimate research into the biology of aging, such as that in which the Pennington Center is engaged. Such research holds great promise for the development of authentic interventions to promote longevity and improve quality of life.

One of the most promising avenues of longevity research involves caloric restriction. Research on caloric restriction dates back to as early as 1935, when Clive McKay, a Cornell Professor, discovered that by "undernutrition" (but not malnutrition) rodents would live longer. He specifically found that by providing a diet containing all the known appropriate nutrients at that time, thereby reducing the calorie level by about 30 percent, could extend life by some nearly 30 percent as well. There was also a delay of

diseases and the animals remained healthy and vigorous. This intervention of caloric restriction has been widely applied to many animal species with comparable results.

More recently, the National Institute on Aging undertook studies of rhesus monkeys in Poolesville, Maryland in National Institutes of Health laboratories, largely under George Roth and Donald Ingram, and at the University of Wisconsin under Richard Weindruch, to explore how caloric restriction influences lifespan. The studies are not complete but the oldest of the surviving animals appear to have an appearance that is younger, as well as certain biological findings related to longevity, such as lower blood levels of insulin, lower body temperature, and slower declines of the hormone DHEA (Dehydroepiandrosterone).

Over the years the concept of caloric restriction has been substantially verified, making it worthy of continuing study to explore its relevance to humans. The purpose, of course, is to uncover the underlying mechanism that can account for how caloric restriction appears to be associated with a lengthening of life and improved health. It is not likely that restricting one's calories by some 30 or 40 percent would be palatable to the average individual. However, should we be able to uncover the underlying mechanism it might be possible to offer an intervention of enormous importance, not just to extend life, of course, but to enhance quality of life.

In the case of caloric restriction and other possible longevity-related interventions, it is important to use longitudinal studies when evaluating their safety and efficacy, like the Baltimore Longitudinal Study on Aging, which is under the aegis of the National Institute on Aging, or the Framingham study, which is supported largely by the National Heart, Lung and Blood Institute. Longitudinal studies provide prospective information, examining subjects over time, in contrast to observational studies, which are short-term.

The studies should also be randomized clinical trials, the importance of which can be seen in the case of hormone replacement therapy. The original study of that intervention, known as the Boston Nurses Study, resulted in the belief that hormone replacement

therapy in women reduced heart disease. But in retrospect it appears that the nurses had better overall health habits, which accounted for the reduction in heart disease rather than the hormone replacement therapy. In contrast, the Women's Health Initiative at the National Institutes of Health was a randomized clinical trial, which included women taking the therapy and not taking the therapy, and the result then unfortunately, was that there was no positive preventive effect of hormone replacement therapy with respect to heart disease and in fact, a danger of some increased risk.

Most longevity-related studies similar to the original hormone replacement therapy study have been observational and carried out over a short time duration, rather than prospective, randomized clinical trials over a period of time. Another example involves the studies at the University of Wisconsin – Milwaukee by Daniel Rudman on human growth hormone, which were limited to some six months. The results suggested increasing muscle mass, decreasing fat and greater elasticity of the skin. But six months is simply too short of a time period to properly evaluate any treatment.

So as I said, it is extremely important to invest at the very outset in carefully evaluating promising interventions to avoid the misuse or inappropriate use of such interventions. Today we have seen sprout up, in various parts of the country, so-called anti-aging medicine clinics which have been based upon unsubstantiated claims of the value of the variety of hormones such as human growth hormone, testosterone and DHEA. The efficacy of these substances as an anti-aging treatment is not only unsubstantiated, but possibly dangerous. For example, in regard to human growth hormone, a recent report from *The Lancet* by professor A.J. Swerdlow and others reported a greater risk of cancer in patients treated with human growth hormone between 1959 and 1985. They found a greater risk of mortality from cancer overall and specifically colorectal cancer and Hodgkins disease. (*The Lancet,* Vol. 1360 No. 9329, July 27,2002) DHEA is another example. It has been observed to decline with aging in humans, and supplementation of DHEA has been promoted as an anti-aging treatment. However, the ultimate meaning or effect of this is unclear because it may be naturally and biologically necessary for DHEA to decline with age.

I do not want to sound critical of legitimate studies to evaluate various products though. We must welcome scientific studies that evaluate dietary supplements, hormones, herbals or any other potentially valuable drugs in advancing healthy aging and length of life. But, it is critical that we are assured of their value as a result of appropriate scientific research, and not unsubstantiated claims.

I would also like to briefly make clear the distinction between anti-aging medicine and geriatric medicine, the latter of which is a legitimate field of medicine that requires great support so that we can be assured that older people receive the high quality medical and social care they deserve.

In closing, the ILC would like to make available to you the results of consensus workshops which we have conducted on a variety of topics relevant to today's hearing. These workshops bring together some of the finest scientists on a particular critical topic. We charge them with four objectives:

1. What can we presently agree upon with respect to the topic at hand?
2. Where we cannot agree, what would be the appropriate research strategy and methods to move the field forward?
3. What can we responsibly tell the public? and finally,
4. Are there policy implications for government, foundations or business?

One recent ILC report of particular interest to the committee today involves anti-aging medicine, which includes both a scientific version and a more popular version that has been supported by the AARP Andrus Foundation. In addition, we have other scientific reports on the results of similar consensus workshops on longevity genes, biomarkers of aging, and maintaining healthy lifestyles, which can be made available to the public and to this committee.

Thank you again for this opportunity to appear before the Committee. Your interest in the important field of longevity research is much appreciated.

The CHAIRMAN. Thank you very much, Dr. Butler, for a very concise and very informative statement, and thank you for your participation. Next as I indicated, we will hear from Dr. Pamela Starke-Reed. She is the Deputy Director of the National Institutes of Health, Division of Nutrition Research Coordination. Before that she was the Program Director of the Biology of Aging Program at the National Institute of Aging.

We are delighted to have you with us.

STATEMENT OF PAMELA STARKE–REED, PH.D., DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH, DIVISION OF NUTRITION RESEARCH COORDINATION, BETHESDA, MD

Dr. STARKE-REED. Thank you. Thank you for the opportunity to appear before you today representing the National Institutes of Health, Division of Nutrition Research Coordination. I would also like to thank you for the challenge of having me summarize nutrition and aging research across the Federal Government in 5 to 7 minutes.

The CHAIRMAN. There is flexibility.

Dr. STARKE-REED. So, therefore, this testimony will include a brief overview of the Federal Government's efforts in this area.

Today, approximately 13 percent of Americans are over 65. By the year 2030, the number of individuals age 65 and older will likely double—reaching 70.3 million or 20 percent of the total population. Of great concern is the explosive increase in numbers anticipated among those most at risk of disease and disability—people age 85 and older. Their ranks are expected to grow from 4.3 million in 2000 to at least 19.4 million in 2050.

With a rapidly aging population, it is critically important to identify ways to maximize the span of good health and thereby improve the quality of life of older people. Nutritional factors hold great promise for realizing this goal. The Federal research efforts in this area of nutrition recognize the need to combine physical activity and diet. I have included some examples of these in the written testimony such as the diabetes prevention program, and the details are in the writeup.

Dr. Butler has already discussed with you some of the background of caloric restriction, so I am not going to repeat that here. But what I would like to talk about is what NIA has been doing, the National Institute on Aging, has been doing recently. In an effort to further elucidate the role of caloric restriction in extending healthy lifespan in humans, in March 1999, the National Institute on Aging and the National Institute of Diabetes, Digestive and Kidney Disease cosponsored a meeting of the Caloric Restriction Implications Advisory Group. In October 2000, based on the scientific recommendations from this group, the NIA and the NIDDK issued research solicitations for exploratory studies of sustained caloric restriction in non-obese persons. Three sites were awarded a research grant: Tufts University in Boston, Washington University at St. Louis and Pennington Biomedical Research Center right here. Collectively, the three projects are known as CALERIE, which stand for Comprehensive Assessment of Long- Term Effects of Reducing Intake of Energy. Government needs to always confuse us with cute little sayings. Briefly, CALERIE projects involve exploratory,

controlled human intervention studies on the effects of caloric restriction interventions on physiology, body composition and risk factors for age-related disease in non-obese persons. The primary goals of the project are to gain knowledge about the effects in humans of sustained caloric restriction on physiology, metabolism, body composition, risk factors for age-related pathologies, progression of age-related changes and the potential adverse effects and to gain knowledge of similarities, differences and interactions between the effects of caloric restriction and physical activity on previous outcomes when employed in interventions to prevent weight gain. The endpoints of CALERIE studies including energy intake and expenditure, physical activity, body composition, endocrine responses, insulin glucose metabolism, cardiovascular function, bone density, immune function, quality of life, and the potential adverse effects of caloric restriction. The study populations of CALERIE projects are non-obese adults with a likely age range of 25 to 60 years. Expected duration of the CALERIE project is 7 years, and it is about to begin the Phase I, or the pilot portion, of the study which is expected to last two years, and I believe you will be hearing a lot more about this from Dr. Bouchard.

Another area of very critical research which the NIA is very interested in right now is the use of dietary supplements. The use of dietary supplements has increased dramatically as the knowledge has increased about the role of nutrient and other bioactive components of food in our health. Although much of the information about the diet and health connection that has driven this trend is related to the reduction of chronic disease in adults, there is belief in the prophylactic use of these substances has been extended to consumers throughout the life span. Dietary supplements encompass a wide range of products. They include vitamins, minerals, amino acid, herbs and other botanicals. They also include dietary substances used to supplement the diet by increasing the total dietary intake.

The amount of scientific data available on the safety and efficacy of dietary supplements varies enormously ranging from folklore to fact. For some supplements recommended levels for the elderly have been established through extensive research and published, but for others, serious negative health consequences can occur. Findings from the CDC's third National Health and Nutrition Examination Survey suggests that 40 percent of the Americans use dietary supplements, and approximately 56 percent of middle-aged and older adults consume at least one supplement on a regular basis.

The problems surrounding the use of dietary supplements include adverse events, interactions with prescription drugs and/or over-the-counter medications, interactions with medical conditions, contamination of the preparations, mislabeling and high cost. Of particular concern for the elderly is the issue of interactions of dietary supplements and prescription medication because the elderly take more prescription drugs than any other age group. For example, the effects of anticoagulant medications commonly taken by the elderly may be adversely affected by coenzyme Q10, gingko biloba, garlic, ginseng, glucosamine and St. John's Wort. Another major issue is the high cost of many dietary supplements. The elderly are

often living on modest fixed incomes, and paying for unnecessary or potentially harmful supplements may present an economic hardship.

But on the other hand, there are significant benefits associated with the use of certain vitamin and mineral supplements. I have given examples of these in the written testimony, but I would like to mention one. There is increasing clinical evidence that the B vitamins such as folic acid, B6 and B12 play a role in preventing blood vessel disease and maintaining normal cognitive function. Some exciting recent work has examined the role of folic acid supplementation in protecting the brain's aging and possibly preventing Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. In a new study, investigators fed genetically engineered mice to develop the plaques that we normally see in Alzheimer's brains. They fed them a diet that included normal amounts of folate, and a second group was fed a diet deficient in this vitamin. The investigators found a decreased number of neurons in one region of the hippo-campus in mice fed the deficient diet. In transgenic mice fed the deficient diet, nerve cells of hippocampus exhibited damage to their DNA. Such damage was not seen in the mice fed adequate amounts of folate.

In another experiment the investigators looked at the effect of a different area of the brain with folate sufficient in folic and deficient diets. Basically what they found was the same thing. In the area of the substantial nigra, which is the area affected during Parkinson's disease, they saw that the folic acid sufficient animals did not show the same damage that the folic acid deficient animals showed. In the subsequent experiments in cell culture, they have suggested that the folic acid deficiency may compromise a neuron's ability to repair its DNA successfully. Based on this research, consuming adequate amounts of folate either in the diet or by supplementation could be beneficial to an aging brain and could help protect it against Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases. However, it should be noted that currently available data, although suggestive, do not establish the role of folic acid in susceptibility to neurodegenerative diseases. Definitive determination of whether folic acid plays a role in Alzheimer's disease or Parkinson's disease will require a completion of controlled clinical trials.

In order to further investigate the role of supplements in preventing or delaying age-associated diseases, the NIA, in accommodation with the NIH Office of Dietary Supplements, will convene a 2-day conference in January 2003 to present current data and research about dietary supplement use in the elderly in both the United States and in the international populations. The goals of this conference are to develop a focused research program in this area.

Mr. Chairman and Members of the Committee, I thank you again for inviting me to review aging and nutrition issues and to highlight some exciting research that is ongoing. I would be happy to answer any questions.

[The prepared statement of Dr. Starke-Reed follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Senate Special Committee on Aging Field Hearing

Pennington Biomedical Research Center
Baton Rouge, Louisiana

August 15, 2002

Statement of Pamela E. Starke-Reed, Ph.D.
Deputy Director, Division of Nutrition Research Coordination
National Institutes of Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of Statement of Pamela E. Starke-Reed, Ph.D.
Deputy Director, Division of Nutrition Research Coordination
National Institutes of Health

Thank you for the opportunity to appear before you today representing the National Institutes of Health (NIH), Division of Nutrition Research Coordination (DNRC). The DNRC is administratively located within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH. Prior to my current position, I was the Director, Office of Nutrition, National Institute on Aging (NIA), NIH. This testimony includes a brief overview of the federal government's current efforts in aging and nutrition research. These efforts include research on caloric restriction, diet and physical activity and recent research activities in dietary supplementation with regard to aging and nutrition.

Today, approximately 13 percent of Americans are over age 65[1]. By the year 2030, the number of individuals age 65 and older will likely double–reaching 70.3 million or 20 percent of the total population[1]. Of great concern is the explosive increase in numbers anticipated among those most at risk of disease and disability–people age 85 and older. Their ranks are expected to grow from 4.3 million in 2000 to at least 19.4 million in 2050[1].

In order to understand the aging process, it is important to identify those factors that affect the overall life span of an organism. It is essential to understand the responsible

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[1]U.S. Census Bureau, Middle Series Projections

physiological mechanisms and to identify ways to slow down age-related changes. Beyond any gains in life span, studies in this area are aimed more importantly at developing interventions to keep older people healthy and free of disease and/or disability as long as possible. Studies in a number of animal models are providing valuable insights into the mechanisms of longevity, yet important questions still remain. For example, it is likely that heredity, environment, and lifestyle all have complex roles in determining a long and healthy life. But is there a maximum human life span beyond which we cannot live no matter how optimal our environment or favorable our genes? And perhaps, most importantly, how can insights into longevity be used to fight age-related diseases and disabilities to ensure a healthy, active, and independent life well into very old age? With a rapidly aging population, it is critically important to find answers to these questions, which could possibly help us identify ways to maximize the span of good health and thereby improve the quality of life of older people. Nutritional factors hold great promise for realizing this goal.

Federally-Supported Aging and Nutrition Research

The NIA at the NIH is the leader in aging research and research on the role of nutrition in aging. However, the NIA is not alone in this endeavor; other Institutes and Centers, other component agencies within the U.S. Department of Health and Human Services, and other federal agencies such as the U.S. Department of Agriculture (USDA) also support research in these areas.

The federal research efforts in the area of nutrition recognize the need to combine physical activity and diet. The Surgeon General's "Call to Action to Prevent and Decrease Overweight and Obesity," which was released in December 2001, encourages the promotion of healthy eating and adequate physical activity. Aging and nutrition researchers were well ahead

of the curve in this line of study. In the early 1990s, scientists at Tufts University, supported by NIA and USDA, conducted a study examining the effect of a nutritional supplement, an exercise regimen or the combination of both, on frailty in the elderly. While nutrition supplementation resulted in a slight decrease in frailty, physical activity provided a better response; however, the best results were obtained with a combination of both nutrition and exercise.

The importance of combining a healthy diet and exercise was again demonstrated in August 2001, when the Diabetes Prevention Program (DPP) clinical trial was halted a year early due to remarkably positive results. The DPP compared three approaches–lifestyle modification, treatment with metformin, and standard medical advice–in 3,234 overweight people with pre-diabetes, a condition in which blood glucose levels are higher than normal but not yet diabetic. About 16 million people in the U.S. have pre-diabetes, which raises the risk of developing type 2 diabetes and cardiovascular disease. Once a person has type 2 diabetes, the risk of heart and blood vessel disease is even greater. It is two to four times that of people without diabetes.

An intervention consisting of diet plus exercise that together produced an average 5 to 7 percent weight loss reduced progression to type 2 diabetes by 58 percent in participants randomized to this lifestyle intervention. Participants in this group exercised at moderate intensity, usually by walking an average of 30 minutes a day five days a week, and lowered their intake of fat and calories. This intervention was most effective in people 60 years and older whose risk of developing diabetes was reduced by 71 percent. Participants randomly assigned to treatment with the diabetes drug metformin had a 31 percent overall lower incidence of type 2 diabetes; however, metformin was most effective in younger individuals. Metformin lowers blood glucose mainly by decreasing the liver's production of glucose.

Changes in diet and physical activity not only prevented the development of diabetes, but also restored normal glucose levels in many people who had impaired glucose tolerance. The DPP, conducted at 27 centers nationwide, is the first major trial to show that lifestyle changes can effectively delay diabetes in a diverse population of overweight American adults with pre-diabetes. The DPP was spearheaded by the NIDDK and co-sponsored by the NIA, the National Institute of Child Health and Human Development, the National Center on Minority Health and Health Disparities, the National Center for Research Resources, the NIH Office of Research on Women's Health, and the NIH Office of Behavioral and Social Science Research, as well as the Centers for Disease Control and Prevention (CDC), the Indian Health Service and the American Diabetes Association.

Caloric Restriction Research

Since the 1930s, investigators have consistently found that laboratory rats and mice live up to 30 percent longer than usual when fed a nutritionally balanced diet that has at least 30 percent fewer calories than they would normally consume. These studies were the first demonstration that the maximum life span of a mammal could be increased.

More recent research has found that these animals also appear to be more resistant to age-related diseases including cancer. Other rodent studies have found that caloric restriction may increase resistance of neurons in the brain to dysfunction and death. In fact, caloric restriction appears to delay normal age-related degeneration of a number of physiological systems in rodents.

Studies on the effects of caloric restriction in higher mammals (monkeys) are ongoing. Preliminary results are promising, including greater resistance to diabetes and heart disease in these animals. Yet, even if caloric restriction is successful in extending primate life span, it is

doubtful that it will ever become a practical and acceptable long-term goal for most humans. However, caloric restriction shows that life span can be altered, prompting research into possible mechanisms.

In an effort to further elucidate the role of caloric restriction in extending healthy life span in humans, in March 1999, the NIA and NIDDK co-sponsored a meeting of the Caloric Restriction Clinical Implications Advisory Group. In October 2000, based on the scientific recommendations from this group, the NIA and NIDDK issued a research solicitation for "Exploratory Studies of Sustained Caloric Restriction in Non-Obese Persons: Physiologic Effects and Comparisons/Interactions with Physical Activity."

Subsequently, three sites were awarded a research grant: Tufts University (Boston, MA), Washington University (St Louis, MO) and The Pennington Biomedical Research Center (Baton Rouge, LA). Collectively, the three projects are known as CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy). Briefly, the CALERIE projects involve exploratory, controlled human intervention studies on the effects of caloric restriction interventions on physiology, body composition, and risk factors for age-related diseases in non-obese persons. The populations of interest in this study include overweight individuals (Body Mass Index of 25.0 to 29.9), other individuals at risk for becoming overweight or obese, and formerly obese persons at risk for recurrence of obesity. The primary goals of the CALERIE projects are to gain knowledge about the effects in humans of sustained calorie restriction on physiology, metabolism, body composition, risk factors for age-related pathologies, progression of age-related changes, and potential adverse effects; and to gain knowledge of similarities, differences and interactions between the effects of calorie restriction and physical activity on the previous outcomes when employed in interventions to prevent

weight gain. The endpoints of the CALERIE studies include energy intake and expenditure, physical activity, body composition, endocrine responses, insulin sensitivity/glucose metabolism, cardiovascular function, bone density, immune function, quality of life, and potential adverse effects of calorie restriction. Study populations in the CALERIE projects are non-obese adults, with a likely age range of 25 to 60 years. The expected duration of the CALERIE projects is seven years. CALERIE is about to begin the Phase I (pilot) portion of the study which is expected to last about two years.

Dietary Supplements and Aging

The use of dietary supplements has increased dramatically as our knowledge has increased about the role of nutrients and other bioactive components of food in health. Although much of the information about the diet and health connection that has driven this trend is related to the reduction of chronic disease risk in adults, belief in the prophylactic use of these substances has been extended to consumers throughout the life cycle. The NIH–along with other government agencies such as the USDA, the Food and Drug Administration (FDA), and the CDC–has had a keen interest in expanding knowledge about: (1) the bioavailability of nutrients and other bioactive components of dietary supplements; (2) the identification of critical gaps in our knowledge about the use of dietary supplements in the elderly; and (3) mechanisms of action whereby dietary supplements might delay aging, facilitate health and prevent the progression of diseases of the elderly.

Dietary supplements encompass a wide range of products. They include vitamins, minerals, amino acids, herbs and other botanicals. They also include dietary substances used to supplement the diet by increasing the total dietary intake. They can be prepared as a concentrate, metabolite, constituent, extract, or combination of any ingredient described

previously, and ingested in the form of a capsule, powder, tablet, liquid, or softgel. The amount of scientific data available on the safety and efficacy of dietary supplements varies enormously, ranging from folklore to facts. For some supplements, recommended levels for the elderly have been established through extensive research and published, but for others, serious negative health consequences can occur.

Findings from CDC's third National Health and Nutrition Examination Survey (1988-1994) suggest that 40 percent of Americans use dietary supplements. Approximately 56 percent of middle-aged and older adults consume at least one supplement on a regular basis. Because of this high frequency of use of dietary supplements in the elderly, the General Accounting Office published two reports in September 2001. Reasons for dietary supplement use include maintenance of overall health, increase of energy, improving memory, preventing or treating illness, and slowing the aging process. The number of scientific studies on the safety or efficacy of these products is limited because FDA approval is not required prior to marketing of dietary supplements, as they are not considered to be either a food or a drug. Problems surrounding the use of dietary supplements include adverse events, interactions with prescription drugs and/or over-the-counter medications, interactions with medical conditions, contamination of preparations, mislabeling, and high cost. Of particular concern for the elderly is the issue of interaction of dietary supplements and prescription medications because the elderly take more prescription drugs than other age groups. For example, the effects of anticoagulant medications commonly taken by the elderly may be adversely affected by coenzyme Q10, gingko biloba, garlic, ginseng, glucosamine, and St. John's Wort. Another major issue is the high cost of many dietary supplements; the elderly are often living on modest fixed incomes and paying for unnecessary or potentially harmful supplements may present an economic hardship.

On the other hand there are significant health benefits associated with the use of certain vitamin and mineral supplements. The evidence supporting the benefit of supplemental vitamin B12 for older adults is so strong that, in 1998, the Institute of Medicine advised all adults age 50 and over to obtain their vitamin B12 from dietary supplements or fortified foods due to a decrease in the body's ability to absorb B12 with aging. There is increasing clinical evidence that B vitamins, such as folic acid, vitamins B6 and B12 play a role in preventing blood vessel diseases and in maintaining normal cognitive function. The need is well established for vitamin D and calcium in the prevention of osteoporosis due to bone mineral loss. Older individuals who do not consume vitamin D-fortified milk should consider consuming 400 International Units of vitamin D per day from a supplement. Similarly, the current adequate daily intake for calcium for adults age 50 and over is 1,200 mg, which–in addition to diet–can only be achieved in some individuals through fortified foods and/or consumption of dietary supplements.

Recent exciting work has examined the role of folate supplementation in protecting the brain against Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. One recent study concluded that high blood levels of homocysteine in people was correlated with nearly twice the risk of developing Alzheimer's disease. In a new study, the investigators fed one group of mice, which were genetically-engineered (transgenic mice) to develop Alzheimer's-like plaques in their brains, a diet that included normal amounts of folate, while a second group was fed a diet deficient in this vitamin. The investigators found a decreased number of neurons in one region of the hippocampus (brain region critical for learning and memory) in the mice fed the folic acid-deficient diet. In addition, in transgenic mice fed a folate-deficient diet, nerve cells in the hippocampus exhibited damage to their DNA. Such damage was not observed in transgenic mice fed an adequate amount of folate. Subsequent

experiments in cell culture have suggested that folic acid deficiency and homocysteine may compromise a neuron's ability to repair its DNA successfully.

Another mouse experiment suggests that folic acid deficiency could increase the brain's susceptibility to Parkinson's disease. Moreover, the scientists discovered that mice with low amounts of dietary folic acid had elevated levels of homocysteine in the brain and blood. It is suspected that increased levels of homocysteine in the brain may exacerbate the cellular damage caused by environmental and other agents to the substantia nigra, an important brain structure that produces dopamine. Loss of dopamine causes the nerve cells to dysfunction, leaving Parkinson's patients unable to direct or control their movement in a normal manner. People who have Alzheimer's disease or Parkinson's disease often have low levels of folic acid in their blood, but it is not clear whether this is a result of the disease or if they are simply malnourished due to their illness.

Based on this recent research, consuming adequate amounts of folic acid–either in the diet or by supplementation–could be beneficial to the aging brain and could help protect it against Alzheimer's disease, Parkinson's disease and possible other neurodegenerative diseases. However, it should be noted that currently available data, although suggestive, do not establish the role of folic acid in susceptibility to neurodegenerative disease. Definitive determination of whether folic acid or homocysteine levels play a role in Alzheimer's or Parkinson's disease will require completion of controlled clinical trials.

In order to further investigate the role of supplements in preventing or delaying age-associated diseases, the NIA, in collaboration with the NIH Office of Dietary Supplements, will convene a two-day conference in January 2003, to present current data and research about dietary supplement use by the elderly in both U.S. and international populations. The goals of

the conference are to develop a focused research program in this area. The issues to be explored include:

- Characteristics of age-related changes in physiology and metabolism.
- Data on dietary supplement use. What segments of the elderly population are using supplements? Which supplements are being used and under what circumstances are they being used?
- Identification of differences reflective of age-related changes that affect physiological functions and bioavailability of nutrients and other bioactive substances, combined with environmental factors that influence behavior (development of attitudes and beliefs).
- Issues and data gaps related to supplement use in the elderly, such as, efficacy, safety, and various types of interactions with prescription drugs, over-the-counter medications, surgical procedures, and disease states.
- Evaluation of current justifications for use, including:
  -effects of dietary supplement use in the elderly on risk factors of chronic disease(s);
  -relative role of diet and/or dietary supplements to meet national health goals for the elderly;
  -the need for supplements in the context of maintaining health and wellness, and/or decreasing the risks of disease.

Mr. Chairman and Members of the Committee, I thank you again for inviting me to review aging and nutrition issues and to highlight some exciting ongoing research. I would be happy to answer questions.

The CHAIRMAN. Thank you very much Dr. Starke-Reed for that testimony. It was interesting that while she was talking about all the supplements I was holding my Centrum Silver and my Calcitrate that I was trying to take while she was testifying. I might reconsider perhaps the benefits of that. [Laughter.]

Thank you very much. Next we will hear from our own Dr. Claude Bouchard, of course, who is the Executive Director of Pennington Biomedical Research Center, and who will tell us and the Committee for the record about some of the work that you are doing right here in Louisiana.

Mr. BOUCHARD. Before I do that, let me give you a copy of my slides so that you will not have to do any body contortions.

The CHAIRMAN. I will move. Thank you.

STATEMENT OF CLAUDE BOUCHARD, PH.D., EXECUTIVE DIRECTOR, PENNINGTON BIOMEDICAL RESEARCH CENTER, BATON ROUGE, LA

Mr. BOUCHARD. Thank you, Mr. Chairman. We at the Pennington Center, a campus of the Louisiana State University System, are particularly honored to welcome you today. We are pleased to have been selected by the Senate Special Committee on Aging as the site for the hearing on the science associated with healthy aging and nutrition.

By the year 2020, there will be an estimated 10 million Americans above the age of 85. This reflects a steady increase in life expectancy. Forty-five percent of people above the age of 85 need some assistance with one or more basic activities of daily living. Today the common life expectancy for males and females is 76 years, and it will be almost 80 years by 2020. Healthy aging depends on a multitude of factors. They are genetic defects having a strong impact on the risk of disease often causing premature death. For instance, the carriers of a severe deficiency in the low-density lipoprotein receptor gene, if untreated, will die around 30 to 35 years of age. However, not all genetic differences exert such a strong impact on health. Most of the time these genetic differences are subtle and cause only a predisposition to the risk of disease or untimely death. We also know that such subtle differences play a significant role in longevity. Twin studies have produced convincing results in this regard, and the fact that old age nonagenarians and centenarians aggregate in families is also evidence for a role of human genetic variation in longevity.

Although biological inheritance is of great importance, the environment in which a person lives, particularly his or her lifestyle within that environment, exerts strong effects as well. For example, someone may have a predisposition to become diabetic but because he or she has a prudent diet, a physically active lifestyle and a healthy body weight, the disease may never manifest itself. A similar line of reasoning applies to hypertension, heart disease, osteoporosis and some types of cancer.

Aging is associated with the loss of physical and/or mental attributes. The central question is whether healthy nutritional habits can prevent the decline in functions commonly seen with aging. The loss of skeletal muscle mass and strength and bone mass is associated with low energy and protein intake. Vitamin D intake also

seems to play a role. Decreases in skeletal muscle and bone mineral mass are associated with frailty and increased risks of falls and fractures. This is significant since almost one quarter of people 65 years of age and older are considered to be physically frail. After 85, one person in two falls into this category.

One of the strongest hypotheses regarding the decline in cognitive function is that oxidative stress is a risk factor. This is supported by studies indicating that levels of intake of antioxidants such as vitamin E, vitamin C, folate, iron and other nutrients are correlated with higher cognitive performance and apparent prevention of cognitive decline with age.

The Recommended Dietary Allowances for the elderly have typically suggested a decrease in total energy intake compared to young and middle-aged adults. However, because of metabolic differences commonly associated with age, supplements of calcium, vitamin D, vitamin B12, and others are recommended. Hence, the paradox.

Even though the prevalence of obesity tends to decline after 65 years, its frequency remains high. This is an important issue since obesity is a risk factor for several common chronic diseases, several of which are quite prevalent in the elderly population.

We would like to emphasize that there are significant interactions and synergy between nutrition and levels of physical activity. Physically active people typically consume more food but are more frequently normal weight than sedentary people. The extra food consumed provides a safety buffer against nutritional deficiency. Nutrition can also interact with medication, and this is potentially of greater significance in the elderly than in young and middle-aged adults.

A word about the Pennington Center. The mission of the Pennington Center is to promote healthier lives through research and education in nutrition and preventive medicine. The Center was established through Doc Pennington's gift of $125 million to Louisiana State University. With the new buildings currently under construction, the Center will enjoy the use of about 500,000 square feet of research space by mid next year. Today the Center has 70 faculty scientists and employs 400 staff and support personnel, and its current expansion program will allow for the doubling of these human resources to about 1,000.

The Center began operating in 1989. Since then more than 200 clinical research projects have been completed and hundreds of basic research projects have been performed. I would like to highlight a few of these clinical research projects that have important implications for nutrition and healthy aging.

The first one is the Dietary Approaches to Stop Hypertension, the so-called DASH Study. DASH was a multicenter investigation of the effects of dietary patterns on blood pressure in adults with high normal to borderline hypertension. Drs. George Bray and David Harsha and other Pennington Center colleagues played a leadership role in this clinical trial. A total of 459 volunteers were randomized to one of three diets: typical American diet controlled on this site, fruit and vegetable diet, and fruit, vegetable plus low-fat diet. Results demonstrated reduction in blood pressure of those of the fruit and vegetable and low-fat diet in both the systolic and

the diastolic pressure. For those with borderline hypertension, the reduction was 11 millimeters of mercury for systolic and more than 5 millimeters of mercury for diastolic.

The DASH Diet parallels the dietary recommendations of the American Heart Association, the U.S. Department of Agriculture, the U.S. Department of Health and Human Services, and the National Cancer Institute and other health organizations, and these findings were applicable to both men and women, ethnic groups, normal tensive and hypertensive and younger and older adults as well.

The Diabetes Prevention Program. The Diabetes Prevention Program is a multicenter NIH-funded clinical trial designed to determine whether the onset of diabetes can be delayed or totally prevented in high-risk individuals. This trial involves 27 centers around the United States. Professors George Bray and Donna Ryan are the leading investigators at the Pennington Center.

The first part of the trial finished in April 2001 when it became clear that one of the treatment arms was much more effective than the others. Among the 3,200 individuals in this study, those randomly assigned to the intensive lifestyle program of diet, exercise and behavioral strategies had a 58 percent reduction in their rate of developing diabetes compared to individuals in the placebo group. A third group receiving the anti-diabetic drug metformin had an intermediate rate of conversion to diabetes. These are the data, 58 percent versus 31 percent. The effectiveness of the lifestyle intervention in reducing the risk of diabetes was demonstrated in men and women, in all ethnic groups and in older and younger Americans.

Regular physical activity translates into important health benefits as shown on this slide which applies to the risk of premature death here. It is also known that physical working capacity, an indicator of fitness, decreases with age. A low physical working capacity can easily compromise personal autonomy. For instance, the capacity to work at a rate equivalent to three to four times the level of energy expended at rest is typically seen as the minimal compatible with physical autonomy. Three to four times would be on the "Y" axis, the number of times that one can expend energy over the resting value. So when we reach above that level here, the personal autonomy is compromised. In a multicenter trial designed to investigate the genetic and molecular basis of the response to regular exercise, about 800 individuals from 200 families of African-American and Caucasian ancestries were recruited and exercised regularly in the laboratory at four clinical centers for 5 months. Considerable individual differences were observed in the progress made under the influence of this physical activity program with some gaining a lot of increased tolerance to exercise by maximum oxygen update measurement. In others, none at all. However, these high responders aggregated in some families, and these others were in other families showing that there is an inherited propensity to benefit from the regular physical activity program.

Thus, there is an inherited capacity to adapt to changes in environmental conditions such as those associated with regular physical activity or with dietary modifications as was shown in another study. Therefore, we would like to suggest that any research effort

designed to define the optimal nutrient and energy intake associated with successful and health aging be undertaken from the comprehensive perspective, one that incorporates physical activity, medication, smoking status, socioeconomic circumstances, family history, as well as biological individuality as defined by the genes.

Herbal Supplements and aging research at the Pennington Center. Many herbal supplements are touted to retard the aging process. Many of these herbal supplements attempt to raise the blood levels of substances to the levels associated with youth. There is no scientific evidence that this approach will retard aging, will increase longevity or improve the quality of life. The Pennington Center is addressing herbal supplements from a more scientific perspective.

The focus of such research is on safety and efficacy. For instance, Drs. Frank Greenway and Steve Smith and their collaborators have been evaluating caffeine and ephedrine in overweight subjects. People taking caffeine and ephedrine lose an average of 7 percent of their body weight, but this is a loss which is totally composed of fat with no loss of muscle tissue. Currently, studies are in progress to study the effect of herbal caffeine and ephedrine on physical strength and endurance. If both strength and endurance were improved in addition to the loss of fat and a protection from muscle loss, then it will be desirable to extend these studies to elderly people.

Caloric restriction. Caloric restriction prolongs life in several species. However, it is not established whether caloric restriction will extend life in humans. Caloric restriction results in loss of weight and tissues and lowers the rate of metabolism. One hypothesis is that caloric restriction lessens the oxidative damage of vital tissues by reducing energy flux and metabolism. Based on these various lines of evidence as was mentioned before, NIA requested application for studies on the role of caloric restrictions in humans, and the Pennington Center was one of the three centers selected nationally. Professor Eric Ravussin is the leading investigator on this research grant that benefits from the collaboration of Professors Andy Deutsch, Don Williamson, Steve Smith, Jim DeLany and other Pennington scientists. They will investigate whether the expected decline in metabolic rate that accompanies caloric restriction will be associated with reduced oxidated stress in tissues and risk factors for age-related metabolic diseases, including cardiovascular and type 2 diabetes.

In addition, they will verify whether combining physical activity and caloric restriction to produce the same caloric deficit alters the changes caused by caloric restriction alone. Finally, the expression of genes involved in energy metabolism and oxidative stress that are known to be associated with longevity in lower organisms will also be assessed.

One of the most accepted theories of aging is an increased release of free radicals, which are unstable molecules that wreak havoc on many substances including DNA. The end result is that individual cells may exhibit increased failure to inactivate free radicals and impair ability to repair DNA damage. One approach to slowing the aging process is to supply the body with ammunition against free radicals in the form of nutritional antioxidants. Nu-

merous studies in other species indicate an increase in longevity is correlated with an organism's ability to effectively cope with free radical damage to DNA. The Pennington Center has one of the most active laboratories for measuring DNA damage in aging tissues, and Professor Andy Deutsch and his collaborators have devised technologies to measure specific DNA alterations that may be a consequence of the aging process, and they will be using it in the caloric restriction study.

Finally, a word about our project on physical and cognitive capacity in non-agenarians. A multicenter study led by Professor Michael Jazwinski from Louisiana State University Health Science Center in New Orleans is investigating the role that metabolic factors play in the aging process. To this end, a population of Louisiana non-agenarians is being assembled. In the context of that study, scientists from the Pennington Center, Professor Ravussin and colleagues, are making a major contribution. They will be measuring resting metabolic rate, total energy expenditure, parameters of oxidative stress, blood protein profile and dietary habits in these non-agenarians. This study will generate a new hypothesis about mechanisms, metabolic pathways and other indicators of the aging process, and these are some of the participants in this particular project.

We would like to take the opportunity provided to us today, Mr. Senator, to formulate a few recommendations for the Senate Special Committee on Aging. First, measures should be taken at all levels of government to ensure that elderly people have access to adequate nutrition. This is of particular relevance since the decrease in appetite typically seen in the elderly can easily result in nutritional deficiencies. Second, measures should be taken to ensure that elderly people have the opportunity to be physically active on a regular basis. This is also of importance as the level of fitness is probably the single most important determinant of autonomy in the elderly. Third, education programs targeting the elderly should be developed to communicate information on nutritional habits, physical activity and proper use of medication. Finally, we would like to recommend the establishment of a national center on nutrition and healthy aging. Its mission would be to improve the health of America's aging population through a focus on research but also on education. This mission would be achieved by: developing basic research programs to determine the molecular and cellular determinants of the adaptation to various dietary regimes and classes of nutrients including herbal and other dietary supplements in the elderly; clinical research programs designed to investigate the impact of various dietary practices and physical activity regimes on physical functions and cognitive abilities in older people, including potential interactions with medication and smoking; behavioral research programs to identify the optimal conditions to induce favorable behavioral changes in the elderly with the goal of reducing morbidity, the risk of premature death, and with the goal of retaining physical and cognitive abilities; integrated research programs to define the interactions among factors such as nutrition, physical activity, medication and genetic individuality; and finally, education and behavioral changes designed to apply the

knowledge developed in the four proceeding programs to the elderly population.

Thank you very much.

[The prepared statement of Mr. Bouchard follows:]

Pennington Biomedical Research Center
LOUISIANA STATE UNIVERSITY

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NUTRITION, PHYSICAL ACTIVITY AND THEIR ROLES IN SUCCESSFUL AND HEALTHY AGING

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We at the Pennington Biomedical Research Center, a campus of the Louisiana State University System, are honored to welcome Senator John Breaux and his staff. We are pleased to have been selected by the Senate Special Committee on Aging as the site for the hearing on the science associated with healthy aging and nutrition. In the brief time allocated to me, I will highlight some of the reasons why our lifestyle and personal choices influence how we age, emphasize the importance of nutritional habits and their close associations with regular physical activity, and provide some examples of the research performed at the Pennington Center in these areas.

By the year 2020, there will be an estimated 10 million Americans above the age of 85. This reflects a steady increase in life expectancy. Forty-five percent of people above the age of 85 need some assistance with one or more basic activities of daily living. This is occurring despite the fact that a reduction in the morbidity associated with aging shortens the period of disablement for most to the last few years of life. Today, the combined life expectancy for males and females is 76 years. It has been projected that life expectancy will increase to almost 80 years by 2020. About 20% of the population will be over 65 in 2020. In Louisiana, there was a 17% increase in the 65 and older age group between 1980 and 1991, while the total population increased by only 0.3%. According to the U.S. Census Bureau, there are currently about 5 people of working age (18-64) for every retiree (65 and over) in Louisiana. This number is projected to be 3 in 2025. These demographic trends jeopardize the existing structures for healthcare delivery and social security. If we are to have an alternative to a dramatic expansion of the nursing home population, we must address the needs of our seniors and improve their ability to remain self-sufficient for a greater portion of their lives.

The improvement of function in seniors is a pressing matter. According to the National Center for Health Statistics, more than 20% of U.S. adults over the age of 65 live in at least partial disability, defined as some degree of difficulty in performing activities of daily living. Furthermore, 14% of these adults receive long-term care. Older adults in the U.S. account for 12% of Medicaid recipients, but they use about 32% of the more than $90 billion spent annually on Medicaid. Astonishingly, over 35% of Louisianans over the age of 65 receive long-term care, which is more than twice the national average. Furthermore, Louisiana has the fourth highest per capita rate of nursing home beds per 1,000 citizens over the age of 85, standing at an

astounding 743 beds per thousand. The economic burden is staggering as Louisiana spends over $563 million each year on long-term care alone.

HEALTHY AGING DEPENDS ON A MULTITUDE OF FACTORS

We already know that there are genetic defects having a strong impact on the risk of disease and often causing premature death. For instance, the carriers of a severe deficiency in the low-density lipoprotein receptor gene, if untreated, will die around 30 to 35 years of age. Those who have inherited two deficient copies of the same gene may die as young as 15 years of age. However, not all genetic differences exert such a strong impact on health and the risk of premature death. Most of the time, these genetic differences are subtle and cause only a predisposition to the risk of disease or untimely death. We know that such genetic differences play a significant role in longevity. Twin studies have produced convincing results in this regard. The fact that old age (nonagenarians and centenarians) aggregates in families is also evidence for a role of human genetic variation in longevity.

Although biological inheritance is of great importance, it does not constitute a full determinism in most cases. The environment in which a person lives, particularly their lifestyle within that environment, exert strong effects as well. For example, someone may have a predisposition to become diabetic but because he or she has a prudent diet, a physically active lifestyle, and a healthy body weight the disease may never manifest itself. A similar line of reasoning applies to hypertension, heart disease, osteoporosis, some types of cancer, and other diseases as well.

A COMMENT ON NUTRITION

Aging is associated with the loss of physical and/or mental attributes. The central question is whether healthy nutritional habits can prevent the decline in functions commonly seen with aging. Sarcopenia, defined as loss of skeletal muscle mass and strength and bone mass, is associated with low energy and protein intake. Vitamin D intake also seems to play a role. This condition is of considerable importance since decreases in skeletal muscle and bone mineral mass are associated with frailty and increase the risk of falls and fractures. This is significant since almost one-quarter of people 65 years of age and older are considered to be physically frail. After age 85, one person in two falls into this category.

The lack of several nutrients has been associated with the decline in cognitive function. One of the strongest hypotheses in this field is that oxidative stress constitutes a risk factor. This is supported by studies indicating that levels of intake of antioxidants such as Vitamin E, Vitamin C, folate, iron and other nutrients are correlated with higher cognitive performance and an apparent prevention of cognitive decline with age.

The Recommended Dietary Allowances for the elderly have typically suggested a decrease in total energy intake compared to young and middle-age adults. However, because of metabolic differences commonly associated with age, supplements of calcium, Vitamin D, Vitamin B12, and others are also recommended.

Even though the prevalence of obesity tends to decline after 65 years, its frequency remains high. This is an important issue to consider in the relation between nutrition and healthy aging. We know that obesity is a risk factor for several common chronic diseases and that age increases this risk. Among these diseases, type 2 diabetes is the most frequently observed, but obesity associated hypertension, coronary heart disease, stroke, osteoarthritis, sleep apnea and other morbidities are also quite prevalent in the elderly. Moreover, excess weight is an important risk factor for premature death although it progressively decreases in importance as the elderly progress from 70 to 80 to 90 years of age.

We would like to emphasize that nutrition is an important component of one's lifestyle but it does not exert its effect independent of other factors and habits. There are significant interactions and synergy between nutrition and levels of physical activity. Physically active people typically consume more food but are more frequently normal weight than sedentary people. The extra food consumed in the physically active elderly provides a safety buffer against nutrient deficiencies. Nutrition can also interact with medication and this is potentially of greater significance in the elderly than in young and middle-age adults. Therefore we would like to suggest that any research effort designed to define the optimal nutrient and energy intake associated with successful and healthy aging be undertaken from a comprehensive perspective, one that incorporates physical activity, medication, smoking status, socioeconomic circumstances and family history.

RESEARCH RELEVANT TO AGING PERFORMED AT THE PENNINGTON BIOMEDICAL RESEARCH CENTER

The mission of the Pennington Center is quite clear and has not changed since its inception. It is simply "to promote healthier lives through research and education in nutrition and preventive medicine". The Center was established through C.B. "Doc" Pennington's gift of $125 million to Louisiana State University in 1980. With the new buildings currently under construction, the Center will enjoy the use of a total of 500,000 square feet of research space by mid-2003. Today the Center has 70 faculty scientists and employs 400 staff and support personnel.

The Center began operating in 1989. Since then, more than 200 clinical research projects have been completed and hundreds of basic research projects have been performed. While it is not possible to review all these studies here, I would like to highlight some of those that have important implications for nutrition and healthy aging.

Dietary Approaches to Stop Hypertension (DASH)

The DASH trial was a multicenter investigation of the effects of dietary patterns on blood pressure in adults with high normal to borderline hypertension (i.e. diastolic pressure between 80 and 95 mm/hg; systolic of less than 160 mm/hg). Drs. George Bray, David Harsha and other Pennington Center colleagues played a leadership role in this clinical trial. A total of 459 volunteers were randomized to one of three diets: 1) a "Typical American" diet (relatively high in fat, low in fruits and vegetables, low in dairy products and low in fiber), 2) a "Fruit and Vegetable" diet (still relatively high in fat, but also high in fruits and vegetables and low in dairy products) and 3) a "Combination" diet (relatively low in fat, high in fruits and vegetables, high in low fat dairy products, and high in fiber and protein).

All participants ate a typical American diet for three weeks before being randomized. Participants ate one meal per day on week days at their local clinical center. All other food was boxed and consumed at home so that no individual used outside food sources for the entire feeding period. Blood pressure was monitored regularly during the feeding trial and the trial lasted eight weeks. Results demonstrated striking reductions in blood pressure for those on the Combination diet. Reductions were -5.5 mm/hg for systolic and -3.0 mm/hg for diastolic pressure for the entire DASH sample. Reductions in blood pressure were consistently noted across gender and ethnic groups indicating wide applicability. For the 30% of the DASH sample with stage 1 hypertension, reductions were of a much greater magnitude. Systolic fell by 11.4 mm/hg and diastolic by 5.5 mm/hg on the DASH "Combination" diet.

The DASH Combination Diet parallels dietary recommendations of the American Heart Association, US Department of Agriculture, US Department of Health and Human Services, National Cancer Institute and

other health organizations. The dietary recommendations of increased fruit, vegetable, and low fat dairy product consumption constitute an important addition to the battery of behavior changes individuals can engage in to lower their blood pressure or hinder the development of dietary hypertension commonly seen with age.

Diabetes Prevention Program

The Diabetes Prevention Program is a multi-center NIH-funded clinical trial designed to determine whether the onset of diabetes can be delayed or prevented in high-risk individuals. This trial involves 27 centers around the United States to assure that the population included a broad range of ethnic groups. Professors George Bray and Donna Ryan are the leading investigators at the Pennington Center.

The first part of the trial finished in April 2001 when it became clear that one of the treatment arms was much more effective than the others. Among the 3,214 individuals enrolled in these 3 arms, the individuals who were randomly assigned to the Intensive Lifestyle program of diet, exercise and behavioral strategies had a 58% reduction in their rate of developing diabetes compared to individuals in the placebo group. A third group receiving the anti-diabetic drug metformin had an intermediate reduction in their rate of conversion to diabetes. The effectiveness of Intensive Lifestyle in reducing the risk of diabetes was demonstrated in men and women, in all ethnic groups, and in older and younger Americans. In fact, the older participants showed a better weight loss than the younger adults. The Pennington Center has been proud to be a part of this important clinical trial that demonstrates that even small weight losses can be beneficial in reducing the risk of developing diabetes in high risk Americans.

HERITAGE Family Study

The Pennington Biomedical Research Center serves as the coordinating center of a multi-center trial, the HERITAGE Family Study, designed to investigate the genetic and molecular basis of the response to regular physical activity in terms of changes in cardiovascular and diabetes risk factors. For this purpose, about 800 individuals from 200 families of African-American and Caucasian ancestries were recruited and exercised regularly in the laboratory at four clinical centers for a period of five months. Subjects were asked not to change their dietary habits in the course of this program and they indicate they were compliant with this requirement. Considerable individual differences in the changes induced by regular physical activity were observed. However, the high responders aggregated in a subset of families while the low responders exhibited the same pattern in another subset of nuclear families. The familial effect for the beneficial response to regular exercise is sufficiently strong for us to undertake a search for the genes and DNA variants associated with this pattern.

The results of this experiment and others performed with dietary intervention indicate that there is an inherited capacity to adapt to changing environmental conditions such as those associated with dietary modifications or with the adoption of a physically active life style. In the aggregate, this research demonstrates that an understanding of the role of specific nutritional patterns will be achieved only if genomics and other basic science domains and technologies are brought into the more applied research paradigms. Incidentally, the HERITAGE Family Study and others that we have been involved in reveal that there is also a genetic predisposition to be physically active or inactive.

Nutrition and DNA Damage and Repair

Numerous theories exist as to the exact causes of aging in humans. One of the most accepted is that humans undergo a progressive deterioration of specific cell components that are essential for generating energy.

Associated with this deterioration is the increased release by these cell components of free radicals, which are unstable molecules that wreak havoc on many cellular substances including DNA. The final outcome of free radical attack on DNA is the generations of anomalies that can ultimately lead to adverse changes such as mutational events. The end result is that individual cells function in ways that they were not originally programmed to behave, including the increased failure to inactivate free radicals and the impaired ability to repair DNA damage in aging cells.

According to this theory, the best approach to slowing the aging process is to supply the body with ammunition against free radicals in the form of nutritional antioxidants. Numerous studies in other species indicate that an increase in longevity is directly correlated with an organism's ability to effectively cope with free-radical damage to DNA.

The Pennington Biomedical Research Center has one of the most progressive laboratories in the nation for measuring DNA damage in aging human subjects. Professor Andy Deutsch and his colleagues have devised technologies to measure specific DNA alterations that may be a consequence of the aging process. They are also poised to determine changes in the ability of specific enzymes and their ability to repair DNA damage that may be compromised in aging cells.

Herbal Supplements and Aging Research at the Pennington Center

Many herbal supplements are touted to retard the aging process. The aging process is poorly understood, but there are certain things in our bodies that change with time. Many of these herbal supplements attempt to raise levels of these substances to the levels associated with youth. There is no scientific evidence that this approach will retard aging, will increase longevity, or improve the quality of life. The Pennington Center is addressing herbal supplements from a more scientific perspective.

As people age, the composition of their bodies change. Even people, who maintain the same weight all their life, have more fat and less muscle as they age. Although weight loss through exercise can give fat loss without muscle loss, weight loss induced by diet is 75% fat and 25% muscle. A safe and inexpensive dietary supplement that would act like exercise in pill form, cause fat loss without the loss of lean tissue, and increases strength and endurance would have the potential to prolong life while increasing its quality. Dr. Frank Greenway and his collaborators at the Pennington Center have been evaluating such a supplement, caffeine and ephedrine, in overweight individuals between the ages of 18 and 60 years of age with the intention to extend this work to the elderly population.

The combination of herbal caffeine and ephedrine initially raises pulse and blood pressure causing the symptoms familiar to someone drinking coffee when not accustomed to doing so. Within eight to twelve weeks, however, the pulse rate, blood pressure and other symptoms go away just as they do for the habitual coffee drinker. Not only do the side effects of caffeine and ephedrine go away, but caffeine and ephedrine also have a long record of safety.

Studies at the Pennington Center have shown that people taking caffeine and ephedrine lose an average of 7% of their body weight that is totally composed of fat with no loss of muscle tissue. Studies are just beginning to test the effect of herbal caffeine and ephedrine on physical strength and endurance. If these studies confirm the theory that strength and endurance increase in addition to the already demonstrated loss of fat and protection from muscle loss, we hope to extend these studies into an elderly population.

Metabolic Adaptations to Two-Year Caloric Restriction

Caloric restriction in rodents from birth or during adult life and in lower species prolongs life. Measurement of surrogate markers of longevity suggests that this may be the case in primates as well. The mechanism(s) responsible, and whether this is the case for humans is unknown. Caloric restriction is associated with several well-known changes in metabolism. It is unknown which, if any, of these changes might be responsible for extending maximum life span. One intriguing hypothesis is that caloric restriction lessens the oxidative damage of vital tissues by reducing energy flux and metabolism. Caloric restriction results in loss of weight and tissues, and lowers the rate of metabolism. Whether there is also a "metabolic adaptation," defined here as a reduction of metabolic rate that is out of proportion to the decreased body size, is a subject of continued debate.

Based on these various lines of evidence, the National Institute of Aging of the National Institutes of Health requested applications for studies on the role of caloric restriction in humans. The Pennington Biomedical Research Center was one of three centers selected nationally to undertake such studies. Professor Eric Ravussin is the principal investigator on this research grant that benefits from the collaboration of many Pennington scientists. He and his colleagues will investigate whether the expected decline in metabolic rate that accompanies caloric restriction will be associated with reduced oxidative stress in tissues, and risk factors for age-related metabolic diseases, including cardiovascular disease and type 2 diabetes. In addition, they will verify whether combining physical activity and caloric restriction to produce the same caloric deficit alters the changes caused by caloric restriction alone. Finally, the expression of genes involved in energy metabolism and oxidative stress that are known to be associated with longevity in "lower" organisms, will also be assessed.

Energy Metabolism and Physical and Cognitive Capacity in Nonagenarians

A multi-center study led by Professor Michal Jazwinski, from the Louisiana State University Health Sciences Center in New Orleans, is investigating the role that metabolic factors play in the aging process. To this end, a population of Louisiana nonagenarians is being assembled. In the context of that study, scientists from the Pennington Biomedical Research Center (Professor Eric Ravussin and colleagues) are making a major contribution. Indeed, the Center is responsible for the recruitment of subjects, making the home visits, and bringing the nonagenarians to the Pennington Biomedical Research Center for testing. Resting metabolic rate, total energy expenditure, parameters of oxidative stress, blood protein profile, and dietary habits are investigated here at the Center. This study will generate a new hypothesis concerning the metabolic pathways and other indicators of the biological aging process.

RECOMMENDATIONS

We would like to take the opportunity provided to us today to formulate a few recommendations for the Senate Special Committee on Aging. These recommendations are brought to the attention of Senator John Breaux and his colleagues because they have the potential to reduce the global burden of chronic diseases in the elderly.

1. Measures should be taken at all levels of government to ensure that elderly people have access to adequate nutrition. This issue is of particular relevance since the decrease in appetite typically seen in the elderly can easily result in nutritional deficiencies.
2. Similarly, measures should be taken to ensure that elderly people have the opportunity to be physically active on a regular basis. This is of particular importance as the level of physical fitness is probably the single most important determinant of autonomy in the elderly.

3. Education programs targeting the elderly should be developed to communicate information on nutritional habits, physical activity, and proper use of medication.
4. We recommend the establishment a National Center on Nutrition and Healthy Aging. Its mission would be to improve the health of America's aging population through a focus on research and education. This mission would be achieved by developing:
    a. Basic research programs designed to understand the molecular and cellular determinants of the adaptation to various dietary regimes and classes of nutrients in aging populations.
    b. Clinical research programs designed to investigate the impact of various dietary practices and physical activity regimes on the preservation of physical functions and cognitive abilities in the elderly. This should take into account the potential interactions with medication and smoking.
    c. Health promoting behavior research programs whose goals would be to identify the optimal conditions leading to favorable behavioral changes in the elderly with the aim of reducing morbidity and the risk of premature death while maximizing the preservation of physical and cognitive functions.
    d. An integrated research program designed to define the interactions among nutrition, physical activity, medication, and other factors important for the elderly and to understand the genetic basis for the variation in individual responses to these factors.
    e. Education and behavior change strategies and programs to apply this new knowledge to the benefit of the elderly.

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The CHAIRMAN. Dr. Bouchard, thank you very much, and I would like to thank all of our Panel Members for some excellent information and suggestions, and information that I think will be very valuable to our Committee.

Let me just start with a couple of questions. I do not know, maybe Dr. Butler, if you go into any bookstore in America, I mean, probably the largest section of publications are books on diet and longevity now, and you can find diets that advocate more fat, some that advocate less fat, some advocating high protein, some low protein. I believe the average person in this country becomes very confused about what is proper and what is healthy. If you add onto those books which many are very, very legitimate, all of the scam artists out there, we had hearings on food additives that are being sold that really do very little.

One of our biggest witnesses who was running a multimillion-dollar—well, actually over a hundred million-dollar—business came before our Committee and took the fifth amendment. He had been in prison before, and he was absolutely a total scam artist. Well, people are spending hundreds of millions of dollars and not really knowing where to go, what is right, what is wrong, what is good and what is bad. Any suggestions for the average American out there that wants to do what is right with regard to this?

Dr. BUTLER. I do think we in science have the responsibility to be clearer to the public that science is an evolutionary process. It is so disappointing and discouraging and confusing when they hear one thing one day and one thing the next. But it is not because of anything other than the fact that the progress of knowledge develops in that way. I think you have heard a very good demonstration of that both from Dr. Starke-Reed and from Dr. Bouchard in terms of how science progresses. That is No. 1.

No. 2, I think Dr. Patrick has been a beautiful example of the very simple fact that probably would be the single major thing one would hope to get out of these proliferation of various books that you referred to, and that is the very simple common sense message of physical activity and small portions of food. The cholesterol hypothesis, the role of certain fats and transacids in the creation of coronary heart disease is very well established through the wonderful work of the National Institutes of Health.

Also, it is important to have a balanced diet in terms of fat and protein and vegetables and carbohydrates, particularly complex carbohydrates. But just not—the one thing mom was probably wrong about was clean up your plate and have a second helping. If we could just have small portions and physically remain active, that would be the single, simple message in a one-page book if we could get somebody to write it and get everybody to believe it.

The CHAIRMAN. When scientists talk about the caloric restrictions, are we talking about just what, eating less, eating smarter, or what are we talking about when we are talking about the value of caloric restriction?

Dr. BUTLER. Well, the original studies of Clive McKay really was an appropriate nutrient diet known at that time for rodents which were in 1935 and 1936, and it was not intended to be anything other than a modest diet as it were. Remarkably these animals live longer.

Now there have been studies on spiders and all sorts of animals that demonstrate this truism. I think the message for the public is that, as I have already said, a modest diet and physical activity. It is energy in, energy out that is so impressive and so important. If we can find what the underlying mechanism is, whether it is the reduction of free radical damage or whatever the mechanism is that counts for the fact that we have this increase, by the way, of a vigorous, healthy life in these animals and delay of disease. It is not just living longer. It is living longer better. If we can find out what that is that is responsible and put that on the market, then we have a fully effective agent.

The CHAIRMAN. Dr. Starke-Reed, do you have a comment on this about what are we talking about? I mean, is it just eating less, or is it eating smarter? I mean, what are the findings that we would be recommending at this time to the American public of what NIH knows about this?

Dr. STARKE-REED. Well, I agree with what Dr. Butler said. I think if we go back to some of the early caloric restriction studies in rodents in particular where they altered the definitions of the diets or the composition of the diets, they were all nutritionally sound, but they altered it to where it was a little bit higher in protein or a little bit higher in carbohydrates or sugar. What they found from changing these diets in these various ways was that it really did not matter. If you were nutritionally sound, you had adequate nutrient and vitamin intake and you had lower calories, total calories, they all had positive effects.

Adding physical activity is absolutely essential. I must mention, because we look at the problem today facing us, the tremendous obesity problem that we are looking at right now, and we are looking at children, very young children, developing type 2 diabetes, and we know that we are not being a very active population. Look at developing countries now. As they become more westernized, they are having a tremendous increase in their obesity problem as well.

These things are not going to lead to healthy aging, so having activity, increasing activity, as well as having smart eating as we say, eating the appropriate things, having a nutritionally balanced diet but lowering the calories is what is going to be probably the best recommendation of all.

The CHAIRMAN. I mean, and we are talking about the obesity problem in this country which obviously leads, as you say, to all types of very serious health problems. I mean, can you evaluate whether it is mostly because Americans just eat too much or we eat the wrong things? I mean, is it more we just eat too much of whatever we eat, or, you know, are we just eating the wrong type of foods containing harmful and fattening things? Does anybody want to comment?

Dr. BUTLER. I would say both.

Dr. STARKE-REED. Well, I would like to say that I do not think there is a definitive study, and as scientists, one would like to base answers on a definitive study. However, I really have to bring into this the physical activity because what is very clear that not only are we changing our dietary habits into very quick, fast, not the most healthy foods being put in front of us, but we are not doing

activity the way we used to do it. We are a very, very sedentary population.

The CHAIRMAN. Can either of you in the time left comment on the valuation between getting the nutrients that we need to live longer, better lives out of the natural foods we eat versus store up on the pills that are supposed to be providing us supplements and the various vitamins that some would probably try and sell you? "You do not really need to eat food. Just come to our general nutrition store and buy everything in the aisles and take all the pills every day and you do not need to eat." I mean, are they valuable but they cannot obviously replace the normal intake? I guess I am talking about food supplements here. I mean, what are their value in general; how important are they; I mean, how much can they be utilized to reduce your caloric intake, or am I only going to eat a very little bit of actual food for breakfast, lunch and dinner, and I am going to supplement it with bottles full of vitamins, so I am going to come out OK? I mean, what is the correlation between the actual, normal regular food we eat and the utilization of supplements to help reach a balanced diet?

Dr. BUTLER. Well, I do think there are supplements that have been demonstrated to be value. For example, folic acid which is now added to cereals and breads has been extremely useful in reducing spina bifida in newborns, and folic acid may also play a role in terms of an agent called homocystine in the body which is related to coronary heart disease. So I do think—and one of the wonderful things about the Pennington Center it seems to me is we have got to dramatically increase the amount of teaching to medical students about nutrition throughout the whole country so that they could give better advice.

Certainly, the recent studies by the National Institute on Aging seem to be pointing to the importance of vitamin E as a preventative with respect to cognitive dysfunction and possibly Alheizmer's disease. So I think some of these "pills" are extremely useful, but as already implied or stated directly by Dr. Starke-Reed, it is so important that this become a consequence of actual science. For instance, if you take too much vitamin E or selenium, which may have their value, you can also wind up with internal bleeding so that there has to be—I guess Aristotle had it right in terms of moderation and common sense. But certainly the degree in which we can get more and more specific so it is not just a smaller amount of food but the right type of added nutrients, it would make a tremendous difference in the quality of life.

But back to Dr. Starke-Reed's point too, only one State in the United States now has required daily physical activity, and that is the State of Illinois. I wish I could say that Louisiana and every one of our 50 States had physical activity for our children. But with computers and with television and with computer games, the chance of kids remaining physically active gets totally denied and left out of the equation of their daily round of activities.

The CHAIRMAN. Well, that is really very, very helpful, I think, and very interesting. I was wanting to follow up on Dr. Bouchard's concepts for a national center of nutrition and healthy aging. I know, Dr. Butler, you were the person who really got the geriatric department started at Mount Sinai Hospital. Out of about 125

medical schools in this country, there are only three that have geriatric departments to teach doctors about specifically aging problems which is an absolutely incredible statement, and you started the one at Mount Sinai, but there are only three. With the vastly growing segment of our population, as Dr. Starke-Reed pointed out, people 85 and older, and 77 million baby boomers getting ready to move into this category of elderly, there will be a lot more people living a lot longer. Yet it seems that we are in a society that is not really focused in on the particular problem of geriatrics and aging and how we can hopefully get people to live longer and also better lives.

Dr. Bouchard, you know, it kind of sounds like to me the concept of a national center on nutrition and healthy aging, just do it right here at the Pennington Center. [Applause.]

Dr. Jenkins is nodding.

Mr. BOUCHARD. I think this is an excellent suggestion. [Laughter.]

The CHAIRMAN. I am throwing these softball questions.

Mr. BOUCHARD. For many reasons, we have the current epidemic of obesity. But we also have now a wave of older citizens millions reaching 85 years and above, where about 50 percent are frail and are losing their autonomy. Nutrition is a part of the latter. Physical activity is also a very strong part of it. The Pennington center has a reputation for working on both, integrating them into research together with the fundamental sciences. The goal is to understand the contribution the general mix with trying to of genetic individuality and the physiology and biochemistry. Such a center with a focus on nutrition would be important because we talk about nutrition and disease and aging, and growth or children for that matter, in terms of vitamins, macronutrients, carbohydrates, lipids and proteins. But that is just scratching the surface.

There are thousands of molecules in food that we know nothing about yet, literally thousands. Some of them have been identified but we do not know their properties. So a center like the one proposed here would remove progressively the mystery surrounding these molecules. In addition to discovering and isolating them, we would test them in cell systems, in animal models, in engineered animals and then eventually in people to see if they have favorable or unfavorable effects when present in large quantities or in deficient levels.

The CHAIRMAN. Dr. Starke-Reed, with the NIH, which is our premier government institute on health, how would a center interact with what you all are doing there or what Dr. Butler is doing at his center? Is that something that is compatible?

Dr. STARKE-REED. I think most of the institutes within NIH have research centers which are dedicated to those specific problems and efforts. So that would fall very much in line with the way NIA does some of those. Can I——

The CHAIRMAN. Dr. Patrick, I do not really have any—do you have another comment, Dr. Starke-Reed? I am sorry.

Dr. STARKE-REED. The one thing that I was going to add to that is I think this is already something which has been in the minds of some of the staff at the NIA, having a specific research center, and that is because when you hear something new that has come

out which is potentially beneficial for aging, it is nice to be able to take it to a place and compare it to a model system or in an organism or animal but with the same hands that have looked at the other things that we know are either good or not good for the aging process.

It is very difficult to compare studies when they are done, even if done within a lab, using different species or different strains depending on whether it is one that is particularly good in aging or bad in aging, and then looking at the outcome. It is very difficult to evaluate whether this product really is having the effect on the aging process desire. Having a center where aging studies are already set up, given you confidence in the results that are generated you trust the reactions that you see in a particular organisms tested there, whether they are good or they are bad. It is very easy to compare it that way.

The CHAIRMAN. I thank you for that. I hope that while you are here—I am sure you have done this before—but have a chance to visit the facilities here and Dr. Butler to see what they are doing.

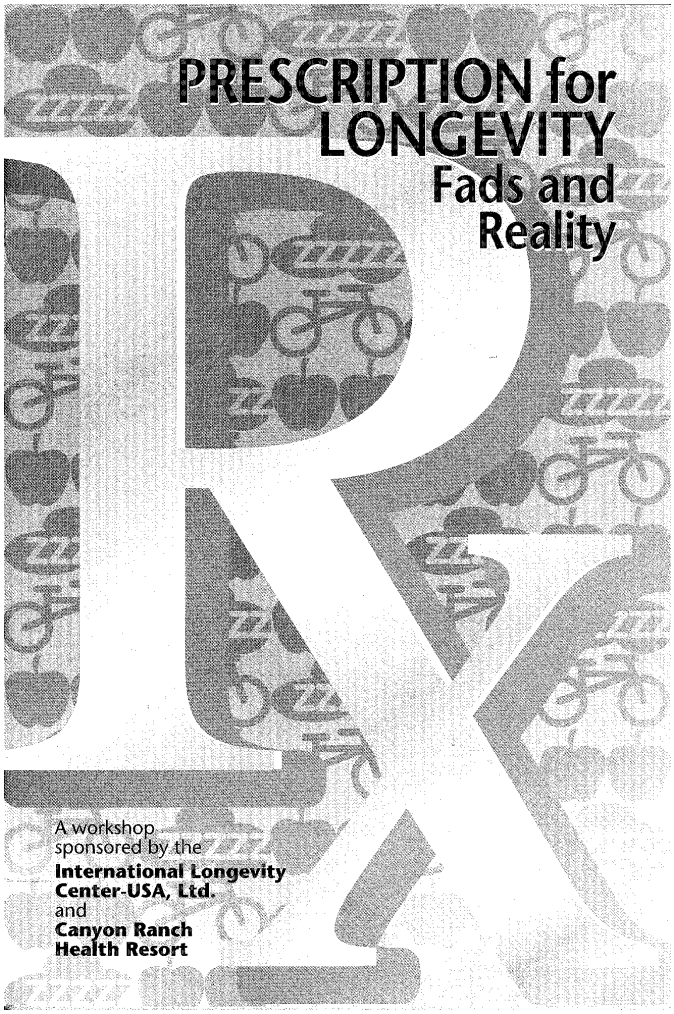
Mr. Patrick, really I am just so happy to have you here. I mean, and the reason we asked you, not only are you a doctor with great credentials in a different field, it is just to show when you practice this type of good, healthy type of living skills really that it does produce positive results, and, I mean, we have had so many people testify before the Aging Committee who are getting up in age, much older than you are. I mean, I had someone who was 92 years old who was actually still working in construction, and he actually worked out in the field. My question was how could he possibly continue to do that type of work in the field. He said, "It is much easier than when I was 40." He said, "When I was 40, I was out there with a shovel digging." He said, "Now I am sitting in this machinery that is air conditioned, and I am just pulling back." He said, "It is a lot easier than when I was 40 years old." He is 92.

So, I mean, you are a good example of that, and we are very pleased that you are here. I want to thank all of our panelists. I think it has been very, very helpful to these people and helpful to the Senate Aging Committee. We are very dedicated to try and help bring about good, honest, solid, scientific research about this issue of aging and to try and separate the legitimate from the illegitimate. There is so much information that is just bogus, and so many people spend an unlimited amount of money trying to look for something that is a miracle, and it is very important that we eat healthy and understand the difference between what is good and what is right and what works as opposed to what does not. I think the Pennington Center is—I am very glad that NIH has saw fit to help with the grant here, and I know that Dr. Bouchard and everybody associated with it is going to do very, very good work.

So we thank all of you for being with us, and that will conclude our Senate Aging Committee hearing. Thank you.

[Whereupon, at 11:24 a.m., the committee was adjourned.]

APPENDIX


PRESCRIPTION for
LONGEVITY
Fads and
Reality
℞
A workshop
sponsored by the
International Longevity
Center-USA, Ltd.
and
Canyon Ranch
Health Resort

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Introduction

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At a workshop held on November 21-23, 1997, and co-sponsored by the International Longevity Center and Canyon Ranch health resort in Tucson, Arizona, fourteen leading gerontologists and experts in nutrition and physical fitness met to discuss what we currently know about how diet, dietary supplements, exercise, and other interventions contribute to better health and increased longevity in adults. This group particularly addressed the question: Which of the much hyped dietary supplements and other interventions are truly effective and safe? The purpose of these workshop discussions was to write a rational prescription with respect to effectiveness and safety, and to develop a research agenda for future work in order to provide facts to replace fads. A summary of our recommendations is presented here.

Many of these recommendations will not come as a surprise to the health-conscious person who exercises regularly, eats a balanced diet, watches his or her weight, and keeps abreast of developments in health research. Sadly, however, this is not a description of the average American. Despite the explosion of information and advice in the print and electronic media, only twenty percent of Americans consume the recommended amount of fruits and vegetables, and only ten percent exercise regularly. That means that the vast majority of Americans are doing little to promote their own health, and this is a poor model for America's children, twenty percent of whom are already decisively overweight.

Perhaps only 30 to 35 percent of individual differences in longevity among humans can be attributed to genes. The remaining 65 to 70 percent may be attributed to lifestyle factors. This offers individuals considerable control over what they can do during their lifetimes to promote health. Today we can encourage general healthy habits that lead to both quality of life and longevity, and occasionally, where there is a family history of certain genetic diseases, we can be more specific. For example, we can advise persons who we know are at risk for developing colon cancer to increase the fibre in their diets and get earlier and more frequent screening procedures by a gastroenterologist. Soon, however, we may have the benefit of full genetic profiles, which will provide detailed information about a person's genetic risk factors and allow us to write an even more customized prescription.

In the meantime, there will undoubtedly be changes in recommendations as the results of new studies advance our understanding of exercise, nutrition, genetics, and other factors that contribute to health and longevity. The fact that prescriptions change over time should not make the public skeptical, however. Rather, this should be looked upon as a sign of the steady, if somewhat up and down, progress of scientific inquiry.

Exercise

If exercise could be put into a pill, we would have the best anti-aging medication available today. Unfortunately, it's not quite so easy. Exercise takes time and commitment — both of which seem to be in short supply in America today. Exercise is a key factor in the prevention of age-related disorders such as cardiovascular disease, type II diabetes, and osteoporosis. Older Americans on average do not get enough exercise, and those who do exercise may not be getting enough if they only engage in light activity. Our prescription for longevity calls for setting aside time most days of the week to engage in moderate intensity exercise, such as brisk walking or cycling. The ideal recommendation is to expend anywhere between 1,000 and 3,000 calories each week in this kind of exercise. That translates, for example, into walking, at minimum, four miles a day, five times a week at an intensity of

200 calories per hour, and, at maximum, slow jogging rather than walking the same distance and frequency, expending around 500 calories per hour.

The prescription also calls for "resistance training," that is lifting and lowering weights that strengthen muscles of the arms, legs, and trunk at an intensity close to maximum effort. Resistance training is a very important part of the entire physical activity prescription because it is the only way to acquire and maintain stronger muscles as we age. Since muscle mass decreases by about 40 percent between the ages of 30 and 70, in part due to inactivity, the importance of strength training can not be over-emphasized.

This is a potent prescription, requiring a lot of exercise. The good news is that you are never too old or out of shape to take charge and begin an exercise program. Clearly, some people will not be able to attain the levels recommended in the exercise prescription because of illness or physical limitations. Experience shows, however, that even stroke victims and patients disabled by arthritis and heart failure can benefit from an appropriate level of exercise. Studies show that even modest physical activity extends longevity.

Diet

There was some controversy among workshop participants about whether dietary supplements, such as vitamin tablets, should be recommended if one's diet contains adequate amounts of fruits, vegetables, and other recommended foods. Most of us agreed that while it is preferable to meet one's daily vitamin and mineral needs through eating the right foods, a daily multi-vitamin tablet ensures adequate intake of certain nutrients that may be deficient in the diets of all too many older Americans.

There was no disagreement, however, about the need to fight obesity and excessive weight gain with increasing age. Overweight becomes an increasing problem in both men and women 40 years of age and older, and it is associated with a number of age-related disorders, particularly cardiovascular disease, hypertension, arthritis, cancer, and diabetes. A combination of reducing caloric intake and

increasing exercise is the safest and the only effective way to achieve long-lasting weight loss. Research has shown that increasing muscle mass through resistance training is an important component to weight loss since muscles of the body, composed of protein, burn more calories than the body's fat stores.

It is interesting to note that restriction of caloric intake is the only known intervention that extends life span and delays age-related disease in a variety of animal species. Since such a restricted diet has never been adequately tested in humans, we do not know yet if it would have the same effects, would be safe, or would be palatable to all people. We do know, however, that modest reductions in total fat, saturated fat, and cholesterol consumption are important for maintaining healthy weight and reducing the risk of age-related disease.

Hormone Treatments

Although so-called "anti-aging" hormones have been much touted in the popular press and health food stores, our experts say that, at this point, the only justifiable hormonal intervention is estrogen replacement therapy for some post-menopausal women, following a careful, customized evaluation by a physician. Other hormone replacement regimes have not yet been thoroughly investigated and may be harmful.

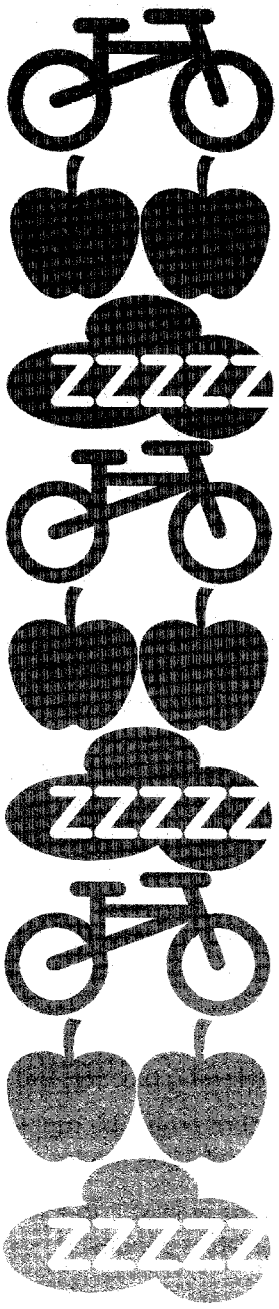
Future Research

How little we know about the most fundamental ingredients of health and longevity throughout life and among older people! For example, we do not know precisely what the healthy weight ranges are for people over 65 years of age, and we do not know what the optimal intake of all macronutrients and micronutrients is for this age group either. Part of the problem is that research in these areas has focused mainly on younger people, and it is assumed that the results of that research apply equally well to older people, which may or may not be accurate.

The workshop participants called for more research on the contributions of diet, antioxidants, sleep, and hormones to overall health and longevity for all age groups. This research becomes crucially important when you consider the fact that the number and proportion of older people will increase dramatically in the next century. We want to insure that our growing older population stays as healthy and productive as possible for as long as possible.

A full report of recommendations from the prescription for longevity workshop follows. We have also provided a glossary to help readers with scientific terms.

Mel Zuckerman, Gary Frost, and the Canyon Ranch staff were our gracious hosts as well as intellectual co-sponsors who contributed to the workshop planning process. Dr. Richard Sprott, co-organizer of the workshop, and Dr. Huber Warner, workshop rapporteur, helped in both the selection of the participants and the development of the agenda. Finally, I would like to thank the participating scientists who shared their insights and helped write the prescription for longevity.



PRESCRIPTION for LONGEVITY
Fads and Reality

Exercise

Americans on the average do not get enough exercise, according to our current understanding of optimal levels for longevity. Although it is not known whether there is an exercise threshold below which little benefit would be provided, a minimum increase of at least 1000 calories per week above sedentary baseline levels is recommended. A level of 2000-3000 calories is preferable, but may not be possible for the very frail old. Both endurance and resistance training are recommended, but the optimal amount of exercise may vary among individuals based on illness, age, physical limitations, etc. Heavy exercise should be avoided in the early morning for people at risk for myocardial infarction, and in the late evening, because it may interfere with the ability to fall asleep. The optimal time is usually the late afternoon for most people.

Diet

The following practices are recommended:

- Calcium should be supplemented, if necessary, to ensure a daily intake of 1200 mg for men and 1500 mg for women.
- Include at least 2 to 4 helpings of fruits and 3 to 5 helpings of vegetables per day.

- Include one multi-vitamin tablet per day to ensure adequate intake of vitamins B_6, B_{12}, C, D, E, and folic acid*, but for the elderly, containing no or low amounts of iron.
- Reduce fat to 30% or less of total caloric intake.

*A diet rich in fruits and vegetables is preferred over dietary supplements, but the diets of many older Americans are deficient in one or more of these micronutrients, and may not supply the optimal amount of some micronutrients, e.g. vitamin E.

Hormone replacement therapy

Estrogen replacement therapy is justified for many post-menopausal women (after consultation with a physician, and in the absence of contraindications). No other hormone intervention is recommended at this time.

Sleep

Older people with sleeping problems should be evaluated by a physician, preferably a sleep specialist, and treated accordingly.

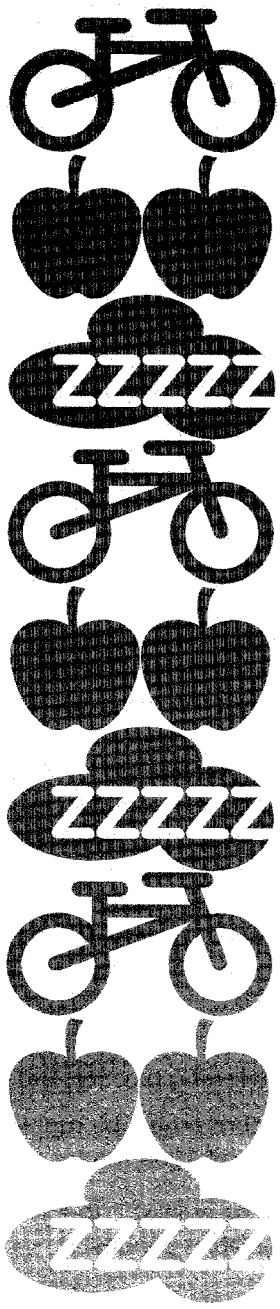
Other

- Regular sun exposure is recommended to maintain adequate vitamin D levels and/or the sleep-wake cycle, although excessive exposure should be avoided to reduce risk of skin cancer and/or melanoma.
- Obesity at any age should be avoided, but it is especially important to prevent excessive weight gain with increasing age.
- Include one children's aspirin (81 mg) per day to reduce risk of myocardial infarction and stroke.
- Add stress reduction/relaxation activities, e.g. exercise, Yoga, Tai Chi, etc.
- Genetic interventions, while promising in animal models, appear to be well in the future, if at all, for humans.

Future Research

Additional research is needed to:

- Identify healthy weight ranges for individuals over 65 years of age.
- Improve our knowledge about optimal intake of both macronutrients and micronutrients for better health for individuals over 65 years of age, and for longevity.
- Obtain reliable biomarkers of human aging to provide information about biological rather than chronological age; not all systems can be expected to age at the same physiological rate.
- Obtain better information on the influence of various antioxidants, both alone and in combination, on overall health and longevity.
- Obtain more information on regulation of sleep in older individuals in order to develop individualized intervention strategies.
- Obtain better information about glucose intolerance and insulin resistance, and how these can be modulated by dietary interventions.
- Define subgroups needing specific hormone replacement therapies, and develop effective and safe hormone-based interventions.
- Develop strategies to educate the public about healthy dietary and exercise habits, including the importance of adequate sleep, and encourage changing behaviors.



Exercise

Physical activity is a complex phenomenon, that to be understood must be characterized by task, intensity, duration, and frequency. On the average, most Americans of all ages do not get sufficient physical activity. Coupled with this observation is the extensive support for the effectiveness of physical activity in the reduction in structural and functional declines that occur with aging. The structural decline is most evident in muscle atrophy which results in a loss of 30% to 40% of the muscle mass between 30 and 70 years of age. The functional declines in endurance and strength are even greater. At any given level of conditioning, a threshold exists for the intensity, duration, and frequency of each task below which no structural or functional benefit is provided. Despite the complexity of this analysis, for most adults, a minimum increase of at least 1000 calories per week above sedentary baseline levels is recommended, which is equivalent to walking four miles a day, five times a week. A level of 2000-3000 calories above baseline is preferable, which translates to jogging rather than walking the same distance and frequency.

Both endurance conditioning for the cardiovascular and respiratory systems, and resistance conditioning for strength, are required to achieve or maintain total body fitness. The optimal type of task, intensity, duration, and frequency of physical activity will vary among individuals based on illness, age, physical limitations, and current state of conditioning. Heavy exercise should be avoided in the early morning for people at risk for having a myocardial infarction, and in the late evening, because it may interfere with the ability to fall asleep. For most people, the optimal time to exercise vigorously is late afternoon.

With increasing age, the muscles atrophy and become weaker and more fatiguable. Superficially, these changes that occur with age appear similar to the changes that occur at any age when a decrease in physical activity occurs. The difference is that the loss in muscle mass and the decreases in strength and endurance

associated with inactivity are totally reversible with subsequent conditioning, whereas the changes associated with aging are observed in both highly conditioned and sedentary people. Importantly, the rate of change is much more rapid when aging is coupled with decreasing physical activity. Under these circumstances, the cumulative losses in muscle mass and function may lead to a loss in mobility, an increased susceptibility to falls and ultimately severe disabilities for older persons. Although under certain conditions growth hormone may increase muscle mass of elderly males, the increase depends on continuing the treatment, which is both expensive and may be accompanied by adverse health effects. Regular physical activity and adequate nutrition provide a much more effective intervention strategy for the elderly to maintain not only an adequate muscle mass, but also muscles that function properly.

Skeletal muscles are capable of performing three types of contractions: miometric contractions when the muscle shortens, isometric when the muscle remains at the same length, and pliometric when the muscle is stretched. For normal function of muscles to be maintained in the elderly, the muscles of the upper and lower limbs and of the trunk must perform each type of contraction frequently and regularly. If muscles do not perform each type of contraction frequently and regularly the muscle fibers that make up the muscle undergo changes that make them more susceptible to injury, and subsequent physical activity is even more difficult. The fibers in the muscles of old people are more easily injured by their own contractions than those in young or adult people. Consequently, regular strength conditioning of muscles is even more important for the elderly than for younger people. The only way to acquire and maintain strength conditioned muscles is to exercise with a diversity of tasks of lifting and lowering activities with light weights that involve the muscles of the arms, legs and trunk. Each individual task for a specific muscle group should be performed 10 times at about 80% of maximum effort and then repeated 3 times with rests in between.

The second requirement of total body fitness for the elderly is to maintain a reasonable level of total body endurance. Total body

endurance which loads the cardiovascular and respiratory systems is achieved most easily and effectively by a total body activity such as walking, jogging, cross-country skiing, skating, or cycling. For a 70 kg person, walking is about 200 calories/hour above baseline, and slow jogging is about 500 calories/hour above baseline. These activities involve the moving of the body mass; consequently, the caloric cost will go up or down proportionately with greater or lesser body masses.

Oxidative Damage and Age-related Disease

All living cells are exposed to oxidative stress in the form of oxygen radicals. In most eukaryotic cells this occurs primarily during the metabolism of oxygen by the electron transport system in the mitochondria. Because of this continuous exposure to oxygen radicals, living organisms have developed robust antioxidant defenses and systems to repair damaged proteins, DNA and unsaturated lipids. Failure to adequately deal with these oxygen radicals is a risk factor for a variety of age-related diseases such as cancer, neurodegenerative diseases, atherosclerosis, and cataract.

The antioxidant defense systems include both non-specific dietary antioxidants such as vitamins C (ascorbic acid) and E, as well as specific enzymes for destroying oxygen entities such as superoxide anion and hydrogen peroxide. Thus, dietary antioxidants provide one possible opportunity for intervention. Ascorbic acid is particularly protective in smokers, and has been shown to reduce DNA damage in sperm. Very recent data suggest that ascorbic acid accumulates in neutrophils during infection, possibly to protect the neutrophils against the very oxygen radicals they generate to kill bacteria.

Another opportunity, as yet largely unexploited, would be to attenuate the rate of production of oxygen radicals by mitochondria. One possible approach is to preserve as much as possible the structural integrity of mitochondria during aging of the cell. Early results in this area of research suggest that maintaining: 1) cardiolipin levels in mitochondrial membranes, and 2) acetyl carnitine synthesis in mitochondria by carnitine supplementation, may both be effective. Lipoic acid and radical scavengers such as

phenylbutylnitrone (PBN) have also been shown to reduce oxygen radical generation by mitochondria.

Diet

Dietary deficiencies are a well-known risk factor for many diseases, including age-related diseases such as cancer, cardiovascular disease, and osteoporosis. Epidemiological data on dietary intakes indicate that in persons whose diet is rich in fruits and vegetables, the risk of a variety of cancers is lowered by one-half. Epidemiological health data also indicate that overweight becomes an increasing problem in both men and women 40 years of age and greater, but especially in women. The percentage of individuals who are overweight reaches as high as 60% in black women in their 50s and 60s. Hypertension also increases steadily across the decades, with up to 60% of men and 80% of women being mildly to moderately hypertensive by their 6th decade.

The workshop participants discussed what is currently known about the role of both micronutrients and macronutrients in human health. Particular emphasis was placed on micronutrients which may be deficient in the diet of older persons. There was consensus that dietary intakes of the following micronutrients may be inadequate in at least 10% of individuals over 70 years of age:

• Vitamin B_{12}	particularly important in synthesis of methionine
• Vitamin B_6	required for many reactions involving amino acids
• Folic acid	required for metabolism of groups containing one carbon atom
• Vitamin D	required for calcium absorption and bone formation
• Calcium	required for bone formation

Current estimates of optimal daily intake by humans are listed in Table 1.

TABLE 1

SUGGESTED DAILY INTAKES OF MICRONUTRIENTS	
Nutrient	**Recommended Total Daily Intake**
vitamin B_6	4 mg
vitamin B_{12}	.01 mg
calcium	1200 mg for men/1500 mg for women
vitamin C	200 mg
vitamin D	400 I.U. for age < 70/600 for age > 70
vitamin E	200 I.U.
folic acid	.4 mg

Research has indicated that supplementation of some micronutrients above the RDA can reduce the risk of age-related disease. For example, high levels of folate and vitamin B_6 have recently been shown to reduce the risk of heart disease in women. Vitamin C has been particularly implicated in the reduction of smoking-induced oxidative damage, whereas vitamin E supplementation has been shown to reduce the risk of cancer and cardiovascular disease. The antioxidant beta carotene may actually increase the risk of cancer, at least in smokers, so its value as a dietary supplement is currently controversial.

Whereas all of the above can be taken as dietary supplements, most experts agree that including generous amounts of fruits and vegetables in the diet is preferred over dietary supplementation. Current recommendations are to include at least 5 servings of fruits and vegetables per day in the diet. A less desirable alternative is to recommend a multi-vitamin pill to the public in general. There is no evidence that this would be harmful, and it is an inexpensive (5-10¢/day/person) and a simple approach. It can be argued that the wide variations among individuals, especially among older adults, require an individualized assessment of dietary deficiencies. The data available to date indicate that use of dietary supplements is greater in women than in men, and that in the American population both men and women increase their use of supplements with increasing age.

Other dietary supplements such as chromium ion (Cr^{+3}), melatonin and dehydroepiandrosterone (DHEA) were also discussed. The use of Cr^{+3} in reducing blood sugar levels, blood pressure and lipid peroxidation in individuals with glucose intolerance and insulin resistance is based mainly on animal experiments. Recent human studies from China show that giving trivalent chromium to type II diabetics lessened the glucose intolerance and reduced the levels of circulating glycated hemoglobin significantly. Many multi-vitamin pills may not contain adequate levels of absorbable Cr^{+3}. The participants agreed that the data in support of including melatonin as a supplement are very weak, and probably flawed. The data for DHEA are also unconvincing, and several laboratories have been unable to replicate some of the published positive results about restoring immune function in mice; DHEA also does not extend life span in mice.

Epidemiological data on macronutrient intake were also discussed. Restriction of caloric intake is the only known intervention which reliably extends life span and delays age-related disease in a variety of animal species. However, this intervention has yet to be adequately tested for either effectiveness or safety in humans. Although countries in which total caloric intake is high tend to have longer-lived populations, this cannot be construed to mean that caloric restriction would not work in humans. It is more likely an expression of the better overall health and better socio-economic status of these populations. Modest reduction of total dietary fat (to no more than 30% of total calories), saturated fat (less than 10% of total calories), and cholesterol (less than 300 mg daily), consistent with the Dietary Guidelines for Americans and the Food Guide Pyramid, is important for achieving and maintaining healthy weight and reducing the risk of heart disease and certain cancers.

Additional research is needed to clarify the health benefits and potential adverse effects of aggressive fat reduction beyond these targets. Additional data are also needed on the effects of modifying fat composition, i.e. saturated vs. monounsaturated and polyunsaturated fatty acids, and altering carbohydrate intake. Excessive reduction of dietary fat, with a concomitant increase in dietary carbohydrate, has been associated in some population groups with adverse effects on biomarkers of chronic disease risk, including

decreased HDL-cholesterol, increased LDL-cholesterol and triglycerides, and insulin resistance. These findings may necessitate a shift in paradigm away from the central focus on dietary fat reduction, to consider the role of dietary fat and carbohydrate composition.

Endocrine Factors

Because hormones are produced in one part of the body and utilized at some other place, and because many hormone levels decrease with age, hormone replacement therapy is an appealing anti-aging intervention (see Table 2). The most successful example so far is estrogen replacement therapy following menopause. This therapy has proven to be not only efficacious and relatively inexpensive in lowering the risk of cardiovascular disease and osteoporosis, but also to have unanticipated consequences, such as a possible lowering of the risk of Alzheimer's disease. A useful intervention, but one less successful over the long term, includes the use of dopamine (levo-dopa) for treatment of Parkinson's disease. Some success in reforming muscle mass has also been reported using growth hormone. Growth hormone levels dramatically decrease with age.

TABLE 2

POTENTIAL HORMONE REPLACEMENT THERAPIES			
Hormone	**Target**	**Known Efficacy**	**Known Side Effects**
Estrogen	Osteoporosis; Heart disease	+++	Yes
Dopamine	Parkinson's disease	++ (short term)	
Acetylcholine	Alzheimer's disease	+	
Growth hormone	Muscle mass	+	Yes
Melatonin	Sleep cycle/other ?	+/?	
DHEA	Several	?	Yes
Testosterone	Several	?	Yes
Insulin-like growth factor I	Several	?	
Cortisol	Stress	?	

+++ very good evidence ++ shows some promise + little evidence

A profound difficulty with these approaches is that it would be extremely difficult to mimic the cyclical changes in blood level for hormones such as growth hormone. This difficulty can lead to undesirable side effects. A conceptual complication is that just because serum concentrations of any circulating hormone decrease with age, this does not mean that restoring them to levels found in younger individuals will be beneficial. Furthermore, many of the therapies of this kind are likely to require individual assessment and surveillance, and thus be expensive and not available to the general population. Thus, only a few of these strategies can be expected to develop into broadly applicable interventions.

Sleep

Well-documented sleep problems for many older adults are insomnia, sleep apnea, and changes in sleep cycles. These problems have different causes, and need to be treated differently. In the case of insomia, which delays sleep until the early morning hours, taking melatonin in the late evening may advance the 24 hour biological clock sufficiently to be useful. However, melatonin is not useful for general insomnia, such as may be caused by sleep apnea. In those individuals who tend to fall asleep early in the evening, bright light in the evening may be useful for delaying the time of sleep onset and waking. Amino acid supplements, e.g. tryptophan, do not appear to be a useful therapy, may actually contain dangerous contaminants, and are not encouraged. Sleep is also associated with growth hormone production, and good sleep cycling may improve growth hormone cyclicity. Thus, this issue is a significant quality of life concern in older adults.

Genetics and Gene Therapy

While it is obvious that differences in life span among animal species have a strong genetic basis, it has been estimated that only about 30-35% of individual differences in human longevity depend on genetic factors. However, with the possible exception of the gene for Werner's syndrome, little is known about which human genes play critical roles in these differences. It can be assumed that longevity is an extremely polygenic trait, and that small differences such as single nucleotide polymorphisms (SNPs) in many genes are partially responsible for individual differences in aging.

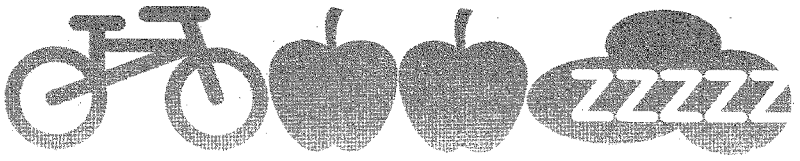
TABLE 3

CANDIDATE AGING GENES
Genes Affecting Life Span in Model Systems

Gene/ Protein	Observation	Organism	Reference
daf2	*daf2* mutation increases life span about 2-fold; homolog of insulin receptor gene	*C. elegans*	Ruvkun. Science. 277: 942-946 (1997)
daf16	*daf16* gene product is required for life span extension by *daf2* mutation; it is a transcription factor whose activity is linked to insulin regulation in humans	*C. elegans*	Kenyon. Science. 278: 1319-1322 (1997) Ruvkun. Nature. 389: 994-999 (1997)
age1 (daf23)	Mutation increases life span 70%; homolog of PI 3-kinase	*C. elegans*	Johnson. Science. 249: 908-911 (1990) Ruvkun. Nature. 382: 536-538 (1996)
sod1 and catalase	Transgenic co-over-expression extends life span 30%	*Drosophila*	Orr, Sohal. Science. 263: 1128-1130 (1994)
lag1	Mutation increases life span 50%	*S. cerevisiae*	Jazwinski. J. Biol. Chem. 269: 15451-15459(1994)
V-Ha-RAS	Mutation increases life span 70%	*S. cerevisiae*	Jazwinski. Mol. Microbiol.4: 2081-2086(1990)
Telomerase	Transgenic expression extends life span of cells grown in culture	*Human fibroblasts*	Harley, Shay, Wright. Science. 279: 349-352 (1998)

Until the existence and frequency of SNPs in the human genome and their impact on aging can be evaluated, an alternate approach is to try to identify and characterize candidate aging genes in genetically pliable model systems such as yeast (*S. cerevisiae*), fruit flies (*Drosophila*), nematodes (*C. elegans*), and mice. Some progress has been made in this comparative biology endeavor. The most notable examples are the *lag1* gene in yeast and the *age1*, *daf2* and *daf16* genes in nematodes. All of these genes code for proteins which play a role in overall metabolism or signal transduction pathways, suggesting there is an important link between longevity and regulation of metabolism (see Table 3). The ability to elucidate how these genetic changes are translated into extended longevity in these model organisms may eventually suggest useful interventions in humans. A somewhat different, but also promising approach, has been to overexpress genes whose products either protect cells against damage or repair damage once it has occurred, e.g. antioxidant enzymes.

Gene therapy is a much heralded but as yet largely unfulfilled strategy for delaying, reducing or preventing age-related human pathology. Few, if any, of the experimental approaches to gene therapy or clinical trials have yet led to a long term successful intervention in humans. The major problems appear to be selective delivery and regulated expression of the gene in the tissue of interest. Most promising are approaches to metabolize, or synthesize and secrete, circulating compounds such as hormones and cytokines. However, interventions practical for large numbers of people are clearly well in the future.



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Glossary of Terms

Acetylcholine (ACh) - Substance released at some nerve endings which passes nerve impulses to the next nerve or initiates muscle contraction. Plays significant role in memory and is reduced in the brains of patients with Alzheimer's disease.

Age-related diseases - Diseases for which age is a major risk factor such as cancer, Alzheimer's disease, cardiovascular disease and osteoporosis.

Amino acids - A group of 20 water soluble organic compounds that have both a carboxyl group and an amino group attached to the same carbon atom, which are the building blocks of proteins. There are nine amino acids which must be included in the diet because they can not be made in the body.

Antioxidants (dietary antioxidants) - Antioxidants react with and neutralize oxygen free radicals generated during normal metabolism. Natural antioxidants include vitamin C, vitamin E, beta carotene, and enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase.

Biomarkers - Biological changes that characterize the aging process. May be a better measure of aging than chronological aging.

Cardiolipin - A phospholipid occurring primarily in mitochondrial inner membranes and in bacterial plasma membranes. Maintaining levels of cardiolipins may help maintain structural integrity of mitochondria in an aging cell.

Carnitine - Carnitine is a compound required for mitochondrial oxidation of fatty acids.

Chromium ion (Cr^{+3}) - A metal ion dietary supplement which has been shown to reduce blood sugar levels, blood pressure and lipid peroxidation in animals.

Contraindications - Any condition, especially a disease or risk factor, which makes a particular line of treatment improper or undesirable.

Cytokines - A soluble factor secreted by cells that acts as a signal to other cells. For example, cytokines interacting with lymphocytes stimulate an immune response.

DHEA (dehydroepiandrosterone) - A weak male hormone produced in the adrenal glands. Precursor to some other hormones, including testosterone and estrogen. Studied for effects on several aspects of aging, including immune system decline, and for its potential to prevent chronic diseases such as cancer, multiple sclerosis, etc.

Dopamine - A hormone which is a precursor to the synthesis of adrenaline. Also functions as neurotransmitter, especially in the brain. It is reduced in the brains of patients with Parkinson's disease.

Enzymes - Proteins that act as necessary catalysts in biochemical reactions.

Estrogen replacement therapy (ERT) - Estrogen is the female hormone produced mainly by the ovaries. ERT is used for the treatment of menopausal symptoms, and the prevention of the long-term effects of menopause, such as osteoporosis and heart disease.

Gene therapy - The use of pieces of DNA to correct pathological conditions and/or genetic defects.

Gerontologist - An individual who does research on various aspects of aging.

Glycation - The process in which glucose molecules combine with proteins, setting in motion a chain of chemical reactions that ends in the proteins binding together or crosslinking. These crosslinks seem to toughen tissues, and may cause some of the deterioration associated with aging (stiffening connective tissues, hardening arteries, clouded eyes, loss of nerve function, decline of kidney function).

Glycosylated hemoglobin - Hemoglobins are the oxygen-carrying pigmented proteins found in erythrocytes formed by the developing erythrocyte in bone marrow. Glycosylated hemoglobin is formed as the result of glycation and is increased in poorly controlled diabetics.

Growth hormone - Secreted in the pituitary gland, stimulates protein synthesis, growth of the long bones in the legs and arms, and the breakdown and use of fats as an energy source instead of glucose. Production of growth hormone may diminish with age.

HDL - High density lipoprotein transports cholesterol from peripheral tissues to the liver; this is considered the "good" form of cholesterol.

Hormone replacement therapy - Use of hormone supplements. Hormones are the body's chemical messengers, produced in organs, tissues and glands. They flow through the bloodstream, and when they come into contact with cells that have hormone receptors, they induce an appropriate physiological response.

Hydrogen peroxide - An "active" form of oxygen which oxidatively damages biological materials.

Insulin resistance - Insulin is the hormone which controls the concentration of glucose in the blood stream. When glucose levels rise, insulin is produced to stimulate the uptake of glucose by tissues. Insulin resistance means that insulin has become less effective at stimulating glucose uptake by tissues.

Isometric - Maintaining uniform length. Isometric exercise is active exercise performed against stable resistance, without change in the length of the muscle.

LDL - Low density lipoprotein transports cholesterol to the peripheral tissues; this is considered the "bad" form of cholesterol, and can lead to cholesterol build-up in the arteries (atherosclerosis). High levels of blood LDL increase the risk of coronary heart disease.

Lipid - Organic compounds which are usually insoluble in water, and are a major component of cell membranes.

Lipid peroxidation - The oxidation of lipids by oxygen free radicals. This oxidation alters the structure and function of cell membranes.

Lipoic acid - A sulfur containing compound which participates in oxidative reactions, but can also act as an antioxidant.

Lysozyme - An antibacterial enzyme widely distributed in body fluids and secretions, including tears and saliva.

Macronutrient - Nutrient required in relatively large amounts, such as carbohydrate, fat, protein, etc.

Melanoma - A tumor arising from the melanocytic system of the skin and other organs. When used alone, the term refers to malignant melanoma.

Melatonin - Hormone synthesized in the pineal gland which declines with aging. In humans it is implicated in the regulation of seasonal changes, sleep, mood, puberty, and ovarian cycles.

Methionine - Naturally occurring amino acid that is an essential component of the diet and necessary for normal metabolism.

Micronutrient - Any essential dietary element only required in small quantities, for example, trace minerals, vitamins, etc.

Miometric - Contractions of the skeletal muscles. A miometric exercise is one in which the muscle shortens.

Mitochondria - Structures within cells that metabolize sugars into energy. They also contain DNA which is damaged by the high levels of free radicals produced in the mitochondria.

Muscle atrophy - The degeneration or withering of muscle due to lack of use or disease.

Myocardial infarction (heart attack) - Occurs when the blood supply to part of the heart muscle is cut off or severely reduced, usually due to coronary heart disease.

Neurodegeneration - Loss of neurons leading to neurological diseases such as Alzheimer's disease, Parkinson's disease, etc.

Neurotransmitter - Substance that mediates the transmission of nerve impulses. Some examples are acetylcholine, adrenaline, noradrenaline, dopamine, serotonin, and glutamic acid.

Neutrophil - A type of white blood cell that releases various substances, including lysozyme and oxidizing agents to destroy bacteria, and eventually engulf them.

Oxidative damage - A wide variety of reactions that can occur when oxygen free radicals attack DNA, proteins and lipids in cells, thus altering both their normal structure and function.

Oxygen free radical - A free radical is a molecule with an unpaired, highly reactive electron. Oxygen free radicals are byproducts of normal metabolism, produced as the mitochondria turn food and oxygen into energy.

Phenylbutylnitrone (PBN) - Radical scavenger that doesn't occur naturally in the body, but has been shown particularly to reduce oxidative damage in the brain.

Pliometric - Contractions of the skeletal muscles. Pliometric exercise involves stretching the muscles.

Radical scavengers - Any of a variety of compounds such as dietary antioxidants and PBN which can neutralize free radicals.

Single nucleotide polymorphisms (SNPs) - Small differences in DNA sequence in genes that may be partially responsible for individual differences in aging.

Sleep apnea - Attacks of failure of automatic control of respiration during sleep. May result in acidosis and vasoconstriction of pulmonary arteries, producing pulmonary arterial hypertension and even death.

Superoxide anion - An oxygen free radical released during normal metabolism in the mitochondria.

Superoxide dismutase (SOD) - An antioxidant enzyme which converts oxygen radicals into the also harmful hydrogen peroxide, which is then degraded by another enzyme (catalase) into oxygen and water.

Triglyceride - A neutral fat synthesized from carbohydrates which stores food energy and releases free fatty acids in the blood as needed.

Tryptophan - An amino acid found in proteins, which is essential for optimal growth in infants and nitrogen equilibrium in adults. Precursor to serotonin, a neurotransmitter that plays a role in depression.

Werner's syndrome - A rare hereditary disorder characterized by premature aging with associated abnormalities, such as dwarfism, cataracts, osteoporosis and hypogonadism.

The International Longevity Center-USA, Ltd.(ILC-USA) is a not-for-profit research, policy and education organization whose mission is to help societies address longevity and population aging in positive and productive ways and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium, which includes centers in the United States, Japan, Great Britain, France and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

The ILC-USA is affiliated with The Mount Sinai Medical Center in New York, which has a strong commitment to health care for older people.

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Concerned with Longevity and Population Aging

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Is there an "anti-aging" medicine ?

Is there an "anti-aging" medicine? is a collaborative effort of the AARP Andrus Foundation and the International Longevity Center-USA. It is based upon the following International Longevity Center workshop reports:

Prescription for Longevity: Fads and Reality

Maintaining Healthy Lifestyles: A Lifetime of Choices

Is There An "Anti-aging" Medicine?

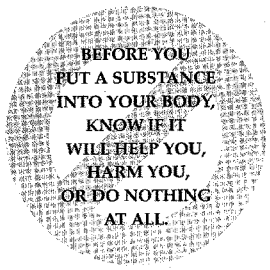
These reports, and the consensus workshops upon which they are based, were made possible through the generous support of Canyon Ranch Health Resorts. Other workshop sponsors include the Kronos Longevity Research Institute and the International Life Sciences Institute.

What is "anti-aging" medicine?

1

Throughout the ages, people have searched for magical potions to reverse the aging process. Alchemists in the Middle Ages spent much of their time trying to change the "lead" of the human body into the "gold of immortality." Ponce de León was searching for the Fountain of Youth when he discovered Florida. And the 19th century was rife with anti-aging potions. In 1889, for instance, a highly respected French scientist named Charles Edouard Brown-Séquard claimed that drinking an extract of crushed dog testicle could restore youth and vigor to old men. (*For more extraordinary anti-aging elixirs, see page 15.*) The point is, over the centuries people have spent fortunes on treatments that promise to control, reverse, or even eliminate the aging process– for a price!

False claims and bogus remedies for treating old age as if it were a disease continue to bombard us today. Anti-aging medicine is a multibillion dollar business that claims to have the "cure" for growing old. This industry markets and sells everything from live cell injections and magnetic contraptions to herbal concoctions, hormonal therapies, vitamin supplements, and fad diets.



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We've all seen these products sold in supermarkets, health food stores, and over the Internet; they are advertised on television, radio, and in direct-mail brochures. Anti-aging remedies range from traditionally recognized nutrients, such as vitamins or minerals, to substances that have no scientifically recognized role in nutrition, such as high-potency free amino acids, herbal remedies, enzymes, animal extracts, and bioflavanoids. They are sold as tablets, capsules, tinctures, poultices, teas, and lotions.

There is so much we don't know about so-called anti-aging medicine, but there is one thing we do know for sure. As we grow older, we have special reasons to think twice before putting these substances in our bodies. For starters, we are often more sensitive to drugs than when we were younger. A younger adult metabolizes and eliminates a drug faster than we do. The dose we take needs to be adjusted to account for the time it takes to metabolize and eliminate a particular substance. *And these substances are not tested by the FDA.*

FDA approval

As one of the nation's oldest public health agencies, the Food and Drug Administration (FDA) is charged with protecting the American consumer. FDA approval is considered the litmus test for safety for almost everything we ingest. 3

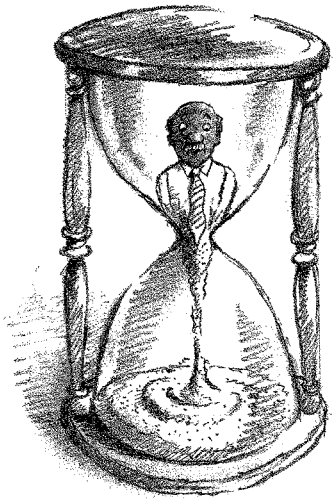
But anti-aging remedies are not well tested– if they are tested at all. In 1994, the Dietary Supplement Health and Education Act designated that these substances were "dietary supplements" and not under the jurisdiction of the Food and Drug Administration. As a result, the FDA does not test vitamins, minerals, herbal remedies, or weight-control substances to ensure they are safe before being sold in the marketplace.

The manufacturers themselves are the only ones responsible for ensuring the safety and effectiveness of their products. They are not required to register with the FDA or get FDA approval before producing or selling their "medicines." Nor does the FDA exercise control over the product label to make sure the information is truthful and is not misleading.

Once a remedy reaches the market, the FDA has the authority to take action if it can prove that the product is unsafe or that the claims are false and misleading. And it often does act in response to complaints.

The Federal Trade Commission (FTC), General Accounting Office (GAO), as well as the U.S. Senate Special Committee on Aging are also beginning to address this issue.

But it is up to us to be well-informed consumers.



Life span is the genetically determined absolute life of a specific animal species under the best of environmental circumstances.

Life expectancy, on the other hand, is the average number of years that a human population of a given age and sex can expect to live under current conditions. Life expectancy increased during the first half of the 20th century because of better sanitation and the widespread use of vaccines. In the 1940s, antibiotics further helped people to live longer. Since the 1970s and 1980s, improvements in longevity have arisen primarily from advances in the medical treatment of people with hypertension, cardiovascular diseases, and stroke. However, while there is no evidence that these developments have actually extended the human life span, they have increased life expectancy.

Hormones

As we grow older our bodies often produce lower hormone levels. It's tempting to believe that if we take substances that raise these levels, we will become young again. It all sounds so simple–replace hormones, such as human growth hormone, DHEA, and melatonin, and find that Fountain of Youth.

But scientific research gives us reason to be skeptical of these claims.

The growth hormone paradox

Growth hormone has a number of functions. It helps develop the long bones in legs and arms. It also helps the body use fat as an energy source. The pituitary gland secretes growth hormone, and as we grow older less hormone is produced.

In 1990, researchers reported that 12 older men who had received injections of growth hormone three times a week over a period of six months became lean and muscular, and their bones became stronger.

However, there have been troubling findings as well. Adults whose pituitary glands over-produce growth hormone have premature heart and lung failure as well as abnormal growth of

other organs and tissues. And laboratory mice who were bred to overproduce growth hormone grew malignant tumors and died younger than mice who had lower-than-normal hormone levels.

In fact, experiments with laboratory animals suggest that decreased growth hormone activity leads to increased life expectancy. Lower growth hormone levels may possibly be an indicator of health.

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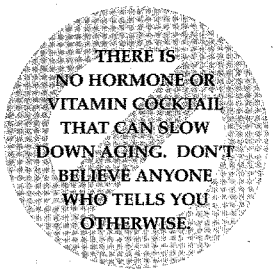


So, although research with hormone replacement has resulted in some positive short-term results, it is clear that negative side effects also may occur in the form of increased risk for cancer, cardiovascular disease, and behavior changes. Necessarily, more studies are warranted before hormone replacement can be considered safe and effective.

Estrogen replacement therapy

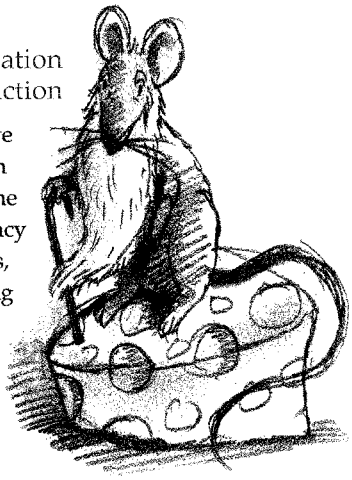
Estrogen is the female hormone produced mainly by the ovaries. Estrogen replacement therapy (or ERT) is used for the treatment of menopausal symptoms and for the prevention of the long-term effects of menopause, such as osteoporosis (thinning of the bones). It may also reduce the risk of dementia in older women.

ERT has had a long history of use by women and has been effective in increasing their quality of life. Until recently researchers believed it also protected women from cardiovascular diseases. But recent studies have raised "red flags" with regard to the usefulness of estrogen for treating or preventing coronary heart disease. The American Heart Association has withdrawn its endorsement for hormone replacement therapy as protection for women against heart disease. And although estrogen may not cause breast cancer, it may promote the growth of existing tumors.

7

While ERT therapy does have some successful history behind it, we have seen that it can also have harmful side effects. Therefore it is up to every woman, in consultation with her physician, to decide whether it is the right drug for her.

Genetic manipulation and caloric restriction



Scientists have succeeded in increasing the life expectancy of laboratory animals (fruit flies, mice, and worms) by identifying "longevity genes." They have also discovered that an animal lives longer when its genes are programmed to produce less growth hormone.

8

As far back as 1935, researchers conducted experiments on laboratory animals to determine if caloric intake affects longevity. The results have shown that laboratory animals live longer and age more slowly when they are fed healthy, very low calorie diets that contain essential nutrients. Animals that began the near-starvation diet in early adulthood extended their lives by 30% to 40%. Scientists observed that this diet delayed the occurrence of age-dependent diseases and disabilities, such as cancers, loss of muscle strength, and cataracts. Since humans are more complicated than lower animals and fruit flies, scientists obviously don't recommend a starvation diet.

What we've learned from these studies–and what translates into healthy old age–is that a low-fat diet rich in grains, fruits, and vegetables lowers our risk for many age-related conditions like cardiovascular disease, high blood pressure, and diabetes. Even more startling, it can cut our risk for a variety of cancers by 50%.

A preliminary study on caloric restrictions in humans is underway at the National Institutes of Health.

Herbal remedies

Herbal remedies include the bark, leaves, flowers, fruits, and stems of a plant. They are available to consumers as teas, powders, tablets, capsules, and as extracts that need to be diluted with water. Herbals are sold in their pure form or in combination with other substances. Very little is known about many of these drugs. While some herbs and botanicals have proven to be safe and effective, here we are concerned with herbs that have not been adequately tested and that may present a health hazard. Several have been associated with serious illness. Check with your physician before taking any of these drugs.

The following list appears in a seminal FDA report entitled *Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Marketplace. (See 7 in References.)*

Herb	Potential negative consequences
St. John's wort	*Interferes with the effectiveness of many prescription drugs used for the treatment of heart disease, seizures, HIV-AIDS. Interferes with medications to prevent transplant rejection and with oral contraceptives.*
Chaparral	*Liver damage.*
Comfrey	*In humans: liver damage. In laboratory animals: cancer, pulmonary, kidney, and gastrointestinal illness. Restricted availability in the United Kingdom, Australia, Canada, and Germany.*
Yohimbe	*Renal failure, seizures, and death.*
Lobelia	*Bronchial dilation; increased respiratory rate; hypotension; has caused coma and death in doses as low as 50 mg.*
Germander	*Liver damage. Sale forbidden in France and restricted in other countries.*
Germanium	*Renal failure.*
Willow bark	*Marketed as an aspirin-free alternative for people who are allergic to aspirin. Contains the same chemical makeup as aspirin and is extremely dangerous for people with aspirin allergy.*

Some Chinese herbal remedies to avoid:

The following herbs are present in products marketed as weight-loss aids and energy boosters:

Stephania/ Magnolia	*Kidney failure.*
Ma huang	*Hypertension, rapid heart rate, stroke, nerve damage, muscle injury, memory loss.*

Vitamins, minerals, and herbs

Vitamin and mineral dietary supplements are considered safe for the general population when taken in doses that don't exceed the recommended dietary allowances (RDAs). Some vitamins and minerals are toxic in high doses. Each vitamin and mineral has its own RDA, and the difference between a safe dose and a toxic dose varies from substance to substance. When in doubt, follow the RDA.

As you consider using an herbal remedy ask yourself these questions:

✍ *Do you know if the substance has side effects?*

✍ *Do you know how the substance will react with drugs you are already taking?*

✍ *Do you know if you have a medical condition or health risk factor that makes it inadvisable for you to take the substance?*

✍ *Do you know if the substance is pure? Are you sure it doesn't contain other substances that may be harmful to your health?*

✍ *Do you know if you're taking the right dose?*

✍ *Do you know the antidote to this drug if you should have a bad reaction?*

11

Serious research vs. scam

A clinical drug trial is research that uses volunteers to test the safety and effectiveness of a drug. It includes men and women from a variety of ethnic and age groups, who are carefully screened to eliminate those with physical conditions that could influence the outcome of the trial. Volunteers in a reputable trial are all given the same dose unless the trial is set up specifically to test a variety of doses. Careful records must be kept and an oversight committee established to ensure that corners are not cut. The drug being tested must come from the same source and be free of other substances that could influence the outcome of the trial. Volunteers in legitimate trials are closely monitored for side effects. *Almost no anti-aging remedy is tested in a clinical drug trial.*

12

Selling anti-aging medicine on the Internet

Most of us have seen the way marketers use the Internet to peddle products that promise quick and dramatic cures for serious diseases. Illegal websites not only sell prescription drugs but unproven anti-aging remedies as well.

Beware of "anti-aging" websites

That offer a new cure or a quick cure for a wide range of ailments;

That claim there is a conspiracy by the government, the medical profession, or research scientists to hide information about a wonder drug;

That use stories of amazing cures and personal testimonials; 13

That make exaggerated or unrealistic claims. If they sound nonsensical, they probably are.

The Federal Trade Commission is cracking down on charlatans on the Internet through its program "Operation Cure All." Meanwhile, it is up to us to exercise caution. Buying an unproven remedy through a website puts us at risk. We may receive a contaminated product or one that contains dangerous substances. At best, we're probably throwing away our money. At worst, we may be endangering our lives.

Five common fallacies about complementary remedies

1 "It couldn't hurt to try it."
Oh, yes, it could! All substances can be toxic if consumed in high enough amounts over a long enough period of time.

2 "I can trust the product label to tell me if I need to exercise caution."
Once again, there is no law that requires manufacturers to include warnings on their labels about potential adverse effects.

3 "It's got to be good for me–it's natural."
Watch out! Just because a substance is found in nature doesn't make it safe. Remember– arsenic is a "natural" substance. Many weight-loss products claim to be "natural" or "herbal," but their ingredients may interact with other drugs, or they may be dangerous for some people.

4 "I trust this product because it has evidence to back its claim."
Some manufacturers print undocumented reports or graphs and charts that can be mistaken for serious research findings. Some research is conducted for only a short time period, so a product's long-term effects are not known.

5 "If the dietary supplement is recalled because it's harmful, I'm guaranteed that it isn't being sold."
The recall of dietary supplements is voluntary. Manufacturers may do their best to comply, but there is no guarantee that all products will be removed.

Just a few of the miracle "cures" that have been peddled throughout the ages:

White Eagle Indian Rattlesnake Oil:
Will cure any kind of pain.

Fatoff Obesity Cream: *Just rub it on.*

Dr. Mixer's Cancer and Scrofula Syrup:
The world-renowned blood purifier for cancer, tumors, erysipelas, abscesses, ulcers, fever sores, goiter, catarrh, rheumatism, piles, and all blood diseases.

Cerralgine Food of the Brain:
A safe cure for headache, neuralgia, insomnia, etc.

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Dr. Bonker's Celebrated Egyptian Oil:
For cramps in the stomach and bowels, and cholera, take 20 drops in molasses or sugar every half hour and at the same time apply externally. For colic and cramps in horses and cattle, give 1 tablespoon in sweet oil.

Dr. Lindley's Epilepsy Remedy:
For epilepsy fits, spasms, convulsions, and St. Vitus' Dance, 1 teaspoon after meals and at bedtime.

Anglo-American Heart Remedy:
For weak hearts, weak blood, weak nerves.

Dr. Shreve's Anti-Gall-Stone Remedy:
For the treatment of stones in the kidney and bladder.

(Source: Food and Drug Administration website. See www.fda.gov.)

The secret to healthy aging

The older we get, the more vulnerable we become to some diseases. But these age-related ailments are not inevitable. So far we've talked about unproven anti-aging remedies. The information presented is based largely on conclusions reached at two scientific workshops held at Canyon Ranch Health Resorts. The results appear in reports entitled *Prescription for Longevity: Fads and Reality* and *Is There An "Anti-aging" Medicine?* (Both are available online at *www.ilcusa.org.*) Now that we know what *not* to do, let's look at what we *can* do to help us age well.

The experts agree: The secret to healthy aging is a healthy diet and moderate exercise. Together with smoke cessation and a low alcohol intake, they offer powerful and proven physical and emotional benefits.

16

At a third Canyon Ranch Scientific Workshop, leaders in medicine, behavorial, and social sciences were brought together to answer a number of important questions: What have researchers found works best for women and men who want to live a healthy lifestyle? What environments are most conducive to healthy lifestyles? What are the best ways for us to achieve and maintain our health goals? What are the most effective kinds of support we can get from the community and society? What areas need further research?

The following is a summary of their report, entitled *Maintaining Healthy Lifestyles: A Lifetime of Choices.* The full report can be downloaded from *www.ilcusa.org.*

Madame Jeanne Calment, who died in 1997 at the age of 122, has the longest documented life span. For most of us though, the average set of human genes appears capable of getting us to at least our mid-eighties, with the majority of that time spent in good health. It has been estimated that about 30% of longevity is determined by genes – the rest is up to us.

17

Environment

Where we live and the people with whom we have daily contact have a powerful impact on our health.

Friends and co-workers

We're all influenced by the attitudes and habits of the people around us. Example: *If a woman smokes but her co-workers, friends, and family members don't, she is more likely to have a stronger motivation to quit than if she is surrounded by other smokers.*

Availability of resources

Community resources, like exercise facilities, parks, and programs that target specific health habits, can motivate us to adopt healthier lifestyles by providing safe, supportive, and convenient environments. Example: *A school with an adult physical education program, a local YMCA, a park, or a community anti-smoking program can support healthier lifestyles.*

Family patterns

Families that have healthy lifestyles provide strong motivation for their family members to establish healthy habits. Example: *A man who joins a gym and begins to show positive results is an automatic role model for his wife and children. Likewise, a woman who quits smoking is a role model for her husband and children.*

18

Ethos of an ethnic group regarding specific healthy habits

Our ethnic identity influences who we are in many ways. People who come from an ethnic community that frowns upon (or simply ignores) exercise, healthy diet, or moderate alcohol intake have to work harder to break old habits. Example: *People who come from a culture whose cuisine emphasizes fried foods will need to seek tasty alternatives to the foods with which they may be most familiar.*

Getting motivated

What motivates us to start a healthy habit and stick with it? Researchers tell us there are many incentives. Among them, vanity, pride, and fear rank high.

Vanity: *Who among us hasn't cringed at the thought of attending a class reunion. We look at ourselves in the mirror and mutter: "If I don't lose weight, my old friends won't recognize me. If I don't lose weight, I won't want my old friends to recognize me!"*

Pride: *Do you really want your kids or grandkids to see you smoking? Is that the kind of role model you want to be?*

Fear: *Never underestimate its motivating power. A critical period in life, whether it's the threat of illness, a life transition, the development of a chronic condition, or the physical decline of a loved one, can be a powerful force for change.*

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The key to success

The experts have found that people are more likely to succeed if they're really ready to make a change and if they have a positive attitude. Men and women who maintain an optimistic outlook are far more likely to attain their health goals than people who believe they will fail before they begin.

Bring a friend. In fact, bring a crowd.

Exercise goes faster when you have a friend or group of friends along. Exercise buddies can motivate each other to show up, keep a spirit of friendly competition going while they exercise, and socialize afterwards.

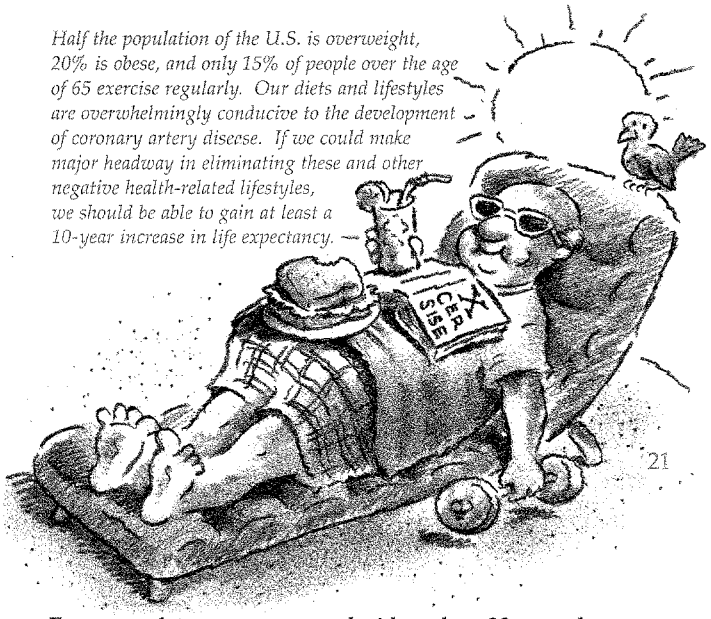
Set a goal

Setting a goal is the first step to making a positive life change. A doctor or fitness trainer can help, but it's important to remember that, ultimately, we are responsible for our bodies and our health. When women and men participate fully in setting their own goals, they're more likely to be motivated to change their health habits than if they accept goals made by another person.

For example, if a man begins a weight-loss program just because his doctor tells him to, the
20 odds are he'll have less success in the long run than if he believes it will benefit him in a way that has personal meaning. He might want to lose weight so he can run a mile without getting winded, because he wants the confidence to find a better job, or because his clothes feel tight.

Make a contract

Before we start out on a new health regimen, we need to ask ourselves: What big goal do I want to achieve? What small goals do I need to achieve so I can reach my big goal? When can I realistically expect to reach my goal? Experts in the field advise us to make a contract with ourselves and to write it down.



For example, a woman may decide to lose 20 pounds over the course of 12 months. She writes a contract committing herself to a goal of significant weight loss, and dates and signs the document. It is her big goal, but she also has smaller short-term goals along the way that serve as guideposts, and she writes these down as well. She may decide that her first goal is finding the time to work out at a gym for one hour three times a week and losing five pounds for her daughter's birthday in three months.

After three months she will have made significant strides in reaching her big goal. She will then revise the contract to reflect a new goal.

She may aim to cut out doughnuts and lose 10 pounds in six months. Her final goal of losing five pounds in three months will be the last step in attaining her big goal, which was to lose 20 pounds. At the end of the year she will have lost the weight and established some important healthy habits.

If she doesn't reach a goal, she will revise her next goal to reflect the situation. For example, if she fell short of her goal to lose 10 pounds and only lost five, her next goal might be to lose another five, and her final goal of losing 20 pounds in 12 months might be changed to 15 months. *Whatever your goals, it's best to keep them modest and attainable.*

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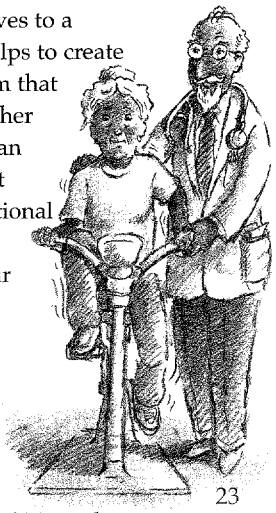
Finally, researchers have found no proof that people who work at reaching several health goals at the same time are more successful than people who focus on one goal at a time. In fact, a new national research effort is currently being conducted at the National Institutes of Health to examine the best ways to introduce and reinforce several behavioral changes at the same time.

Create a personal plan of action



When we commit ourselves to a healthier lifestyle, it helps to create a personalized program that reflects who we are rather than a fantasy program designed for an Olympic star. We need to think about where we live, our physical and emotional makeup, where we work, our friends and family, and the way we spend our free time. Consider the following:

What serious health problems must I address?
Always see a physician before beginning a serious workout program.

What activities do I enjoy?
If you absolutely hate jogging, making ambitious plans to run at the local track may not be the best idea.

What activities can I get to easily from where I work or live?
Swimming is fun, but if the indoor pool is half an hour away and always crowded you may soon tire of the effort it takes.

What kind of activities can I afford?
Are the fees for the tennis court within your budget?

When can I find time?
What days and times are most convenient?
What alterations can you make in your schedule?

The neighborhood

Our communities may be the best support we have for a new health program. City hall and almost any local paper offer readily available community resources. These include gymnasiums, walking clubs, and programs to quit smoking or lose weight.

The workplace

There is a growing body of evidence to suggest that a healthy lifestyle program in the workplace can be very beneficial. For instance, many companies now have effective smoking-cessation programs. Here are some other suggestions to help you begin or stick with a health program.

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Establish a routine that is based on a modest modification of everyday work activities:

- ❑ *Walk up the stairs instead of taking the elevator.*
- ❑ *Snack on fruits and raw vegetables instead of snacking at the candy machine.*
- ❑ *Use a break to do stretching exercises in the office or outside in a public park instead of lighting up a cigarette.*
- ❑ *Consider biking or walking to work.*
- ❑ *Take advantage of low-fat, lower-calorie alternatives that are now available in many company cafeterias.*

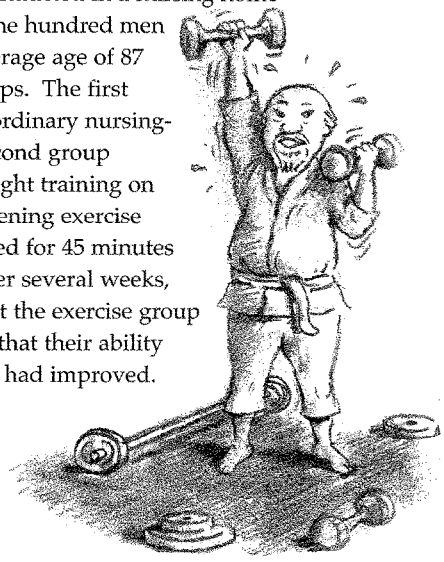
When is exercise really exercise?

In recent years, there has been a shift away from an exclusive emphasis on intensive aerobic exercise, and today health professionals encourage a wide range of physical activities. We can ride bikes, run, walk, and take dance classes for aerobic fitness. In addition, many find that yoga, tai chi, and other classes that emphasize stretching or upper-body strength are beneficial.

Weight training

Weight training that is done in moderation can be beneficial for women and men of all ages. One very important study conducted in a nursing home illustrates this point. One hundred men and women with an average age of 87 were split into two groups. The first group continued to do ordinary nursing-home activities. The second group received supervised weight training on thigh and knee strengthening exercise machines. They exercised for 45 minutes three times a week. After several weeks, researchers reported that the exercise group was less depressed and that their ability to walk and climb stairs had improved. (*See 6 in References.*)

25



Staying motivated

We've set our goals, signed a contract with ourselves, and embarked on our journey to health. But then it rains. Or we get too busy to work out. Or we go out to dinner with friends and eat much too much. How do we get back on track? How do we stay motivated? Here's what the experts suggest:

Keep a record of your progress. For example, note how far you walk or run each day by wearing a pedometer, which is an inexpensive electronic clip-on device that monitors movement.

Write down what you eat every day in a journal.

26 Visit your doctor six months after you begin your program. The results, in terms of weight loss, lower blood pressure, and general well-being, will almost certainly be evident, even if you've experienced a setback.

Overcoming setbacks

Setbacks are part of the normal process of any changes we make in our lifestyle. A relapse is not a failure, and a setback can be used to strengthen our resolve. It can motivate us to take steps to avoid falling into the same trap in the future. The speed with which we reach our ultimate goal is less important than the direction we're heading. *Remember, it's never too late to start, and it's always too soon to quit!*


GOOD
HEALTH
STOP SMOKING
HEALTHY DIET
MORE ACTIVE

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AARP
www.aarp.org

AARP Andrus Foundation
www.andrus.org

Alliance for Aging Research
www.agingresearch.org

International Longevity Center–USA
www.ilcusa.org

The National Council on the Aging
www.ncoa.org

National Institutes of Health
www.nih.gov

Federal Drug Administration
www.fda.gov

National Center for Complementary and Alternative Medicine, NIH
www.nccam.nih.gov

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D17692

Is There An "Anti-aging" Medicine?

An Interdisciplinary Workshop of the
INTERNATIONAL LONGEVITY CENTER–USA

Co-Sponsors:
Canyon Ranch Health Resort
Kronos Longevity Research Institute
Columbia University College of Physicians and Surgeons Center for the Study of Society and Medicine

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Preface

Until the mid-twentieth century, doctors dismissed medical conditions that affected older people by adding the prefix "senile" or "postmenopausal" to the diagnosis. It was presumed that diseases to which older adults were particularly vulnerable, such as osteoporosis and the dementias, were unavoidable attributes of the aging process, and healthy aging was something of an oxymoron.

It is true that a gray area exists between aging and disease, and that aging per se predisposes us to increasing vulnerability to disease. For the past fifty years, research in gerontology has focused on differentiating the normative processes of aging from the effects of debilitating diseases. Today, there is much promise in research that can yield information about the underlying biology of aging and longevity. Government, private philanthropy and pharmaceutical companies should be eager to invest. Unfortunately, serious research is being mistaken for "anti-aging" medicine, which argues that we already know the mechanisms of aging and the appropriate interventions to slow, stop, or even reverse the aging process. Government and private philanthropy, which together are the largest sources of funding for research on the basic biology of aging, believe "anti-aging" medicine, as it currently exists, to be pseudoscientific and commercially exploitative.

"Anti-aging" medicine is a multi-billion dollar industry in the U.S. It is under the control of non-scientists who use terms like "virtual immortality" and "an ageless society" to attract customers to untested remedies that have not withstood the rigors of serious clinical trials. It must be noted that testing the efficacy of anti-aging remedies presents special problems because we do not have valid biomarkers of aging. That is, we cannot objectively measure age. We have no objective biological measurement that applies to everyone at a specific age. And we have no instrument to measure age objectively in that we lack the age-measuring equivalent of a scale that gives objective weight, or a thermometer that gives objective temperature.

The very concept of "anti-aging" medicine goes against the last fifty years of work in gerontology, devoted as it was to differentiating normative and natural aging processes from diseases such as arteriosclerosis. The idea of "anti-aging" also promotes and reinforces ageism. It puts a profoundly negative connotation on the very occurrence of aging, emphasizing its negative and depleting aspects. For example, this concept denies all that is enriching and positive about aging in the psychosocial sphere.

In contrast, we prefer that longevity researchers adopt the term "longevity medicine". Longevity medicine expresses the intention of the field to extend life within what appear to be genetically determined limits, through control of the myriad diseases that afflict humanity, and through direct intervention in the biological processes of aging. Longevity medicine should apply to all means that would extend healthy life, including health promotion, disease prevention, diet, exercise, cessation of tobacco use, as well as advanced medical care and new discoveries that result from basic research. It also suggests the ultimate possibility of identifying and even manipulating those genetic factors that may influence the genetically determined limits of the species.

Acknowledgements

This is the fifth Canyon Ranch - International Longevity Center (ILC) Scientific Workshop. We are grateful to Canyon Ranch for its intellectual support, and for providing us with a wonderful venue for our scientific consensus workshops. Mel Zuckerman and Gary Frost have been unflagging in their enthusiasm. We thank the Kronos Longevity Research Institute for its contribution to this workshop, with special thanks to Dr. S. Mitchell Harman, the Institute's director, who took an active intellectual role. Special appreciation goes to Dr. Huber Warner for his remarkable efforts in preparing this report. Thanks also to Nora O'Brien, M.A., for her assistance in coordinating the workshop and preparing this report, to Judith Estrine for editing and supervising its publication.

Finally, we want to express our great appreciation to Dr. David Rothman, Columbia College of Physicians and Surgeons, who acted as co-chair, for his important contribution to the success of this workshop.

These closed workshops are modeled after National Institutes of Health Consensus Workshops. We bring together scientists on particular critical topics to decide what can be agreed upon, and when a consensus is reached, to develop a research agenda. The participants are then asked to determine what information should be provided to the public, and finally, what messages are pertinent to policy-makers at the foundation and governmental level. Previous workshops have included *Prescription for Longevity, Maintaining Healthy Lifestyles, Achieving Cognitive Vitality with Aging, and Biomarkers: From Primitive Organisms to Man.*

The Workshop Report

INTRODUCTION

The purpose of this workshop was to discuss what is known about existing and possible future interventions that can slow, stop, or reverse aging in humans, and how to promote this area of scientific research and medical practice.

It is reasonable to assume that slowing human aging would also delay the onset of a wide variety of age-related diseases, significantly increasing both health and longevity. However, there is as yet no convincing evidence that administration of any specific compound, natural or artificial, can globally slow aging in people, or even in mice or rats. Claims to the contrary (e.g., that a specific hormonal or vitamin preparation can slow down aging), are not based on evidence. Such claims are thus misleading to the public, and these substances should not be administered or used. These claims also obstruct the search for greater understanding of the biology of aging, and the eventual development of authentic longevity-promoting interventions of documented safety and efficacy.

WHAT IS "ANTI-AGING" MEDICINE?

Butler et al. (2000) recently discussed what distinguishes "anti-aging" medicine from geriatrics. In the recently published *Biomarkers of Aging: From Primitive Organisms to Man* (International Longevity Center, 2001), aging was defined as a process that progressively converts physiologically and cognitively fit, healthy adults into less fit individuals with increasing vulnerability to injury, illness, and death. Within this framework, an "anti-aging" medicine could be simply defined as any intervention that delays the development of age-dependent pathology and other adverse age-related changes that are not officially listed as diseases.

HISTORICAL CONTEXT

The first serious attempt to develop a scientific prescription for longevity was published in the eighteenth century by a German physician named Christopher Hufeland. In a collection of diet and lifestyle recipes called *Makrobiotik*, he described what could be considered the earliest effort to intervene in order to slow down aging (Hufeland, 1797)). However, it was not until the nineteenth century, when the French physician Jean Martin Charcot published his *Clinical Lectures on Senile and Chronic Diseases*, that the science of gerontology itself was born (Charcot, 1881). In this work Charcot clearly outlined the scientific principles for the practical study of aging. It was the first truly scientific treatise describing the physiology, organ changes, and diseases associated with aging.

Unfortunately, this early developmental process took a giant step backward some twenty-two years later, when Charles Edouard Brown-Sequard claimed that by drinking an extract of crushed dog testicles, old men could recover the strength and vigor of their youth (Brown-Sequard, 1889). Although Brown-Sequard was sincere in his belief that this testicular elixir was rejuvenating, his "experiment," and the subjective reports it

generated, were the preamble to a long chain of quacks, snake oil salesmen, and charlatans who have successfully sold "anti-aging" potions to the public—a practice that continues to this day (Olshansky and Carnes, 2001). False claims and bogus remedies for treating old age as if it were a disease have flooded the marketplace ever since. Yogurt cures, enema regimens, live-cell injections, magnetic contraptions, skin creams, herbal elixirs, glandular extracts, procaine preparations, hormonal therapies, vitamin supplements, fad diets, and exercise programs, all claiming to combat aging, are familiar to everyone. The hype is everywhere, and it seems to be increasing.

CAN HUMAN LIFE EXPECTANCY BE EXTENDED?

Not everything we hear about anti-aging is hype. Although the question remains open, the present
2 state of our knowledge is somewhat encouraging, based on results with laboratory animals. In this document we will use the term "life expectancy" to refer to the mean length of life for a population of individuals, whether people or animals. The term "maximum life span" will be used to define the longest-lived member of a population.

A variety of interventions can increase by 30% or more the life expectancy and maximum life span of rodents, fruit flies, and nematodes. The first scientific evidence for this came from the longevity-extending caloric restriction experiments in rodents by McCay et al. (1935), as described below. Caloric restriction experiments in non-human primates were initiated in 1987, and although survival data are not yet available, results on delay of age-related changes appear to mirror those observed in rodent experiments (Cefalu et al., 1997; Wanagat et al., 1999; Roth et al., 2000). Supporting evidence comes from several genetic manipulations, primarily those manipulating responses to insulin and IGF-I in nematodes and fruit flies, and growth hormone in rodents (Table 1). In these experiments, a 30% to 40% extension seems to be the rule.

However, it was the general consensus of the workshop participants that neither similar genetic modifications nor voluntary caloric restriction per se deserves serious consideration as an intervention in humans. The importance of these research findings in animals is as follows: 1) they show that aging can be slowed dramatically in model systems through simple means; and 2) they point to promising directions for research that could lead to practical pharmacological approaches to effectively decelerate aging, and thus prevent or delay the occurrence of a wide range of age-related pathologies in people. For example, discovery of a mimetic of caloric restriction—a pharmacological agent that imitates the underlying mechanism of caloric restriction—would be a major step forward.

Unfortunately, in the absence of actual data, some have predicted human life expectancy reaching well into the hundreds (Klatz and Goldman, 1997; Rose, 1999). In fact, the longest well-documented human life span is that of Madame Jeanne Calment, who died in 1997 at the age of 122. Moreover, the current life expectancy in the United States is only 78 years for females and 73 years for males. This was possible in the twentieth century only because of improvements in medical technology, nutrition, and sanitation (Wilmoth et al., 1998), and behavioral modification, such as reduction in smoking. Further extension will almost certainly require biomedical intervention to delay age-related pathology and disease. However, Olshansky et al. (1990) calculated that eliminating deaths from cancer, heart disease and stroke would only raise human life expectancy into the upper nineties.

In contrast, an achievable life expectancy in the future for Caucasian women in the U.S. might be as high as 113 years (81 x 1.4 = 113) (Figure 1).

This calculation is based on the available rodent data with either caloric restriction or genetic modifications, when applied to humans.

We already know that life expectancy of this scope is possible in isolated cases, either through good health behavior, good genes, and/or good luck, but it is likely that further extension will require biomedical technology beyond that currently available. If extrapolation of the caloric restriction paradigm from rodents to humans is valid, this also suggests that large increases in life expectancy to 150 years or more in humans, as often suggested by anti-aging entrepreneurs, may be unrealistic without major new insights into the molecular mechanisms of aging (Olshansky et al., 2001).

The concern that extending life expectancy will also lead to prolonged illness and disability seems unwarranted, based on the results obtained with rodents, and recently with humans. In a retrospective study of a New England population sample, 88% of centenarian females and 100% of centenarian males were functioning independently at age 92. At age 97, 45% of the women and 75% of the men were still functioning independently (Hitt et al., 1999). These findings are consistent with James Fries' compression of morbidity hypothesis proposing that, as the limit of human life expectancy is approached, the onset and duration of lethal diseases associated with aging will be compressed toward the end of life (Perls, 1995; Vita et al., 1998).

CURRENT STATE OF KNOWLEDGE

During the twentieth century, life expectancy for the average person increased dramatically in developed countries. For females in Japan, for example, life expectancy at birth more than doubled, increasing from 36.9 years in 1900 to 81.9 years in 1990 (Goldman and Takahashi, 1996). In the first half of the century, most of this increase was due to a decline in infant mortality. Between 1900 and 1960 the drop in mortality from infectious diseases became the most important factor increasing life expectancy. During the 1970s and 1980s, improvements in longevity arose primarily from mortality reductions in the major chronic diseases (i.e., hypertension, cardiovascular disease, and stroke) in middle and older-aged persons. Clearly, modern technology has made great strides toward improving human health and enabling greater numbers of people to survive into old age. This is one of the great achievements of modern technology and medical science. However, it must be pointed out that there is no evidence that any of these laudable developments has actually extended the maximum human life span. To equal this rate of progress in the twenty-first century, humankind must achieve retardation of the rate of human aging itself, and extension of the maximum life span.

3

CURRENTLY AVAILABLE HUMAN BEHAVIORAL INTERVENTIONS

Based upon Danish and Swedish twin studies, the average set of human genes appears to be capable of getting us to at least our mid-eighties, with the majority of that time spent in good health (Perls et al., 1999). However, life expectancy at birth in the United States is approximately 10 years less, largely because we are failing to take advantage of our genetic potential for longevity by engaging in practices which lead to premature onset of the degenerative diseases associated with aging. Half the population is overweight, 20% is obese, and only 15% of people over the age of 65 regularly exercise. Our diets are overwhelmingly conducive to the development of coronary artery disease, and far too many of us still use tobacco products. If we could make major headway in eliminating these and other negative health-related

behaviors, then those of us who live in industrialized countries should be able to experience at least a ten-year increase in average life expectancy, approximating that of Okinawans or Seventh-Day Adventists (Fraser and Shavlik, 2001; Willcox et al., 2001). The cost savings and health-related benefits to individuals and to our society in the near future would be tremendous.

Medical researchers and physicians do have good evidence for interventions that can prevent or delay specific diseases and disabilities, including some that typically appear in old age. These include drug treatments (e.g., the use of antibiotics to prevent peptic ulcers and stomach cancer, lipid-lowering drugs for persons with high LDL cholesterol, and anti-hypertensive agents for those with high blood pressure); nutritional recommendations (such as increases in fiber, fruits, and vegetables); and alterations in behavior (e.g., use of seat belts and sunscreens, adoption of regular exercise programs, and avoidance of tobacco products). Adherence to such recommendations deserves strong endorsement, but even if everyone followed them, their net effect on longevity and the diseases of aging would be far smaller than the effect of an intervention that slowed down the aging process to the degree now routinely possible in laboratory animal models (Figure 1).

4

CALORIC RESTRICTION

Extensive research on a paradigm known as caloric restriction or dietary restriction has clearly shown that it is possible to retard the rate of aging and also extend both the life expectancy and maximum life span of animals. Richard Weindruch and Roy Walford summarized early research in this field (1988). Subsequent studies have served to confirm and extend these findings, and to suggest possible mechanisms by which caloric restriction may alter biological aging (Dhahbi et al., 1999; Hansen et al., 1999; Lee et al., 1999; Lal et al., 2001). Caloric restriction is accomplished by restricting the caloric intake of an animal far below the level that the animal would consume voluntarily. This extends life expectancy by 30% to 40% if initiated in early adulthood, and by about 20% if initiated in early middle age. As long as a diet maintains adequate content of essential nutrients, it is not a "poor" diet, but a low-calorie, healthy diet. Caloric restriction does this presumably by slowing down the rate of aging. Concomitantly, it delays the occurrence of a wide range of age-dependent diseases and disabilities, such as cancers, immune senescence, cognitive decline, loss of muscle strength, and cataracts.

These caloric restriction results provide evidence that aging can be decelerated and longevity extended in mammals, and many studies predict that human longevity is equally plastic. The concern that extending longevity will also lead to prolonged illness and disability seems unwarranted, based on results obtained with rodents. Caloric restriction could thus be classified as a true anti-aging intervention.

GENETIC MANIPULATION

Increases in life expectancy in animal models can also be accomplished genetically (see Table 1; Miller, 1999; Guarente and Kenyon, 2000). At least 15 different genetic manipulations induce life extension in organisms such as fruit flies, nematodes, and mice. Although genes that regulate life expectancy have been identified, it is not always obvious how the proteins coded by these genes are involved in the determination of longevity. However, there are similarities between the longevity genes identified in mice and those identified in invertebrates. For example, growth hormone induces the production of insulin-like growth factor I (IGF-I) in mammals.

Table 1

Genetic Interventions That Extend Life Span in Animal Models

GENE	ORGANISM	BIOCHEMICAL FUNCTION	COMMENTS	REFERENCES
v-Ha-RAS	Yeast	Oncogene	Life expectancy varies with level of expression	Chen et al. (1990)
lag1	Yeast	Ceramide signaling pathway	Mutations increase life expectancy	D'mello et al. (1994) Guillas et al. (2001)
sir2	Yeast	NAD-dependent histone deacetylase	Activity required for normal life expectancy; over-expression increases life expectancy	Imai et al. (2000) Kim et al. (1999)
daf2	Nematode	Insulin/IGF-I like receptor	First step in insulin-like signaling pathway; mutations increase life expectancy	Larsen et al. (1995) Kimura et al. (1997)
age1/ daf23	Nematode	PI-3-kinase	Operates in insulin-like signaling pathway; mutations increase life expectancy	Johnson (1990) Morris et al. (1996)
daf16	Nematode	Transcription factor	Expression required for life expectancy extension by daf2 or daf23 mutations	Lin et al. (1997)
tkr1	Nematode	Tyrosine kinase	Over-expression increases life expectancy and resistance to stress	Rikke et al. (2000)
InR	Fruit fly	Insulin/IGF-I like receptor	First step in insulin-like signaling pathway; mutations increase life expectancy	Tatar et al. (2001)
chico	Fruit fly	Insulin receptor substrate	Second step in insulin-like signaling pathway; mutations increase life expectancy	Clancy et al. (2001)
mth	Fruit fly	Transmembrane protein	Partial loss of function increases life expectancy and resistance to stress	Lin et al. (1998)
indy	Fruit fly	Dicarboxylic acid transport protein	Partial loss of function increases life expectancy	Rogina et al. (2000)
SOD-1	Fruit fly	Cu/Zn-superoxide dismutase	Over-expression increases life expectancy	Sun and Tower (1999) Parkes et al. (1998)
p66shc	Mouse	Not known	Mutations enhance resistance to apoptosis and increase life expectancy	Migliaccio et al. (1999)
pit1/ prop1	Mouse	Required for pituitary development	Mice are deficient in GH, prolactin and TSH, and grow slowly; mutations increase life expectancy; delayed immune and collagen aging	Brown-Borg et al.(1996) Bartke et al. (2001) Flurkey et al. (2001)
ghr/bp	Mouse	Growth hormone receptor	Loss of function increases life expectancy	Coschigano et al. (2000)

Mutations that decrease production, either of growth hormone or its receptor in mice, increase life expectancy, as do mutations that decrease insulin-like signaling in nematodes and fruit flies. Thus, insulin and/or IGF-I signaling appear to be involved in life expectancy determination in a wide range of phylogenetically distant animal species (Kenyon, 2001). The results reported recently by Flurkey et al. (2001) suggest that growth hormone deficiency also delays age-dependent collagen cross-linking and several age-sensitive indices of immune system status. They demonstrate that a single gene can regulate life expectancy and the timing of both cellular and extracellular senescence in a mammal.

ANTIOXIDANT INTERVENTION AND RESISTANCE TO STRESS

Another common thread is the association between increased life expectancy and increased resistance to stresses such as heat, reactive oxygen species, or ultraviolet light. While there are theoretical reasons for suspecting that increased stress resistance contributes to increased life expectancy, this has not been proven. Moreover, the relevance of these findings to human aging is not known. Some epidemiological studies have suggested that dietary supplementation with vitamin E reduces the risk of cancer (Heinonen et al., 1998), and cardiovascular disease (Knekt et al., 1994; Kushi et al., 1996; Stephens et al., 1996), but such observations are not universal (HOPE, 2000). Furthermore, the longevity-extending potential of vitamin E in animal studies remains equivocal (Anisomov, 2001). McCall and Frei (1999) have concluded in a review that, "except for supplemental vitamin E, and possibly vitamin C, being able to significantly lower lipid oxidative damage in both smokers and non-smokers, the current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans." The only robust finding that a pharmacological antioxidant can extend longevity in an animal model system is the report of Melov et al. (2000) that EUK-134, a compound with both catalase and superoxide dismutase activities, significantly extends longevity in nematodes.

HORMONE REPLACEMENT THERAPY

It is tempting to believe that restoration of hormone levels to those that exist in young persons should universally be a desirable goal. In principle, the approach is simple, but hormone replacement therapy is a long-term proposition, possibly continuing for the rest of a patient's life. The circulating levels of growth hormone, testosterone, estrogen, dehydroepiandrosterone (DHEA), and other hormones decrease with age. Supplementation with melatonin or DHEA, or injection of growth hormone, have all been promoted in highly visible books (Pierpaoli et al., 1995; Regelson and Colman, 1996; Klatz and Kahn, 1998). However, the question of whether melatonin levels also decrease with age is controversial (Zeitzer et al., 1999). While some hormone replacement strategies have been shown in clinical trials to modify some of the physiological attributes associated with aging, negative side effects occur frequently with those interventions shown to have some benefit, such as growth hormone. Negative side effects occur less frequently with interventions for which evidence of benefit is either absent or equivocal, such as DHEA. Although the epidemiological data are overwhelmingly positive regarding some health benefits of estrogen replacement therapy (see next section), a recent study has raised a concern about ovarian cancer after long-term use (Rodriguez et al., 2001a). In another example, Anisomov et al. (2001) reported that melatonin supplementation increases the mean life expectancy of mice by about 5%. However, they also found that spontaneous tumor incidence increased in

the melatonin-treated mice. Thus, more research is needed to determine the proper application of hormones within a clinical environment.

ESTROGEN REPLACEMENT THERAPY (ERT)

ERT is a special case of hormone replacement therapy and deserves particular attention here because of its long clinical history and apparent record of success in increasing both the length and quality of life in postmenopausal women. Estrogen is particularly recommended for preventing osteoporosis, but it may also reduce the risk of dementia (LeBlanc et al., 2001) and cardiovascular disease (Ettinger et al., 1996; Grodstein et al., 1997; Schairer et al., 1997; Grodstein et al., 2001). The incidence of cardiovascular disease in women is negligible before menopause and increases dramatically thereafter. Some epidemiological data have suggested that ERT reduces the occurrence of coronary artery disease, and possibly cerebrovascular disease, by 25% to 50% in treated women compared with non-users (Grodstein et al., 2000). These findings are supported by evidence that estrogens have a beneficial effect on cholesterol metabolism and deposition, contributing to the inhibition of atherosclerotic plaque formation in arterial walls. It has been estimated that favorable changes in plasma lipids may account for approximately 25% of the cardioprotective effect of estrogens, and that other effects are therefore likely to be important. The influence of estrogens on carbohydrate metabolism, atheroma formation and cardiovascular hemodynamics may also play an integral role in the overall beneficial effect of the hormones. Animal and human studies have shown that the administration of estrogens leads to a restoration of endothelial function, an increase in cardiac output, an increase in arterial flow velocity, a decrease in vascular resistance, and a decrease in systolic and diastolic blood pressure (Rajkumar et al., 1997). However, the conclusion that estrogen protects postmenopausal women against cardiovascular disease is now being questioned, based mainly on experiments examining secondary prevention in women with pre-existing heart disease (Manson and Martin, 2001). These studies have caused the American Heart Association to withdraw its support for ERT as a preventive measure against coronary vascular disease (*Washington Post*, 2001).

Media reports have led to some insecurity and concern about the use of sex steroids after menopause. The incidence of breast cancer increases continuously with aging, and although ERT does not induce breast cancer, it may promote the growth of existing tumors. It has been estimated that if 1000 women start ERT at the age of 50 and continue for five years, two more cases of breast cancer will be diagnosed within the next 20 years (Birkhauser, 2000). This small increase of morbidity is not accompanied by an increased mortality due to breast cancer, but a small increase in ovarian cancer has been recently reported (Rodriguez et al., 2001a). Nevertheless, the data available today show a clear decrease of total mortality up to the age of 75 years in women using ERT (Rodriguez et al., 2001b). The gain in quality of life and the reduction in all-cause mortality that is associated with ERT have prompted many practitioners to proclaim ERT to be the first true anti-aging therapy. However, no results have yet been reported of randomized studies comparing effects of ERT with placebos, beginning at the menopausal transition, in women with no known pre-existing coronary heart disease or dementia. Until such data become available, the risks versus benefits of ERT are likely to remain controversial. Therefore, the risks and benefits of long-term ERT need to be evaluated individually for each subject.

Figure 1
Aging Research: Biggest Bang for the Buck?

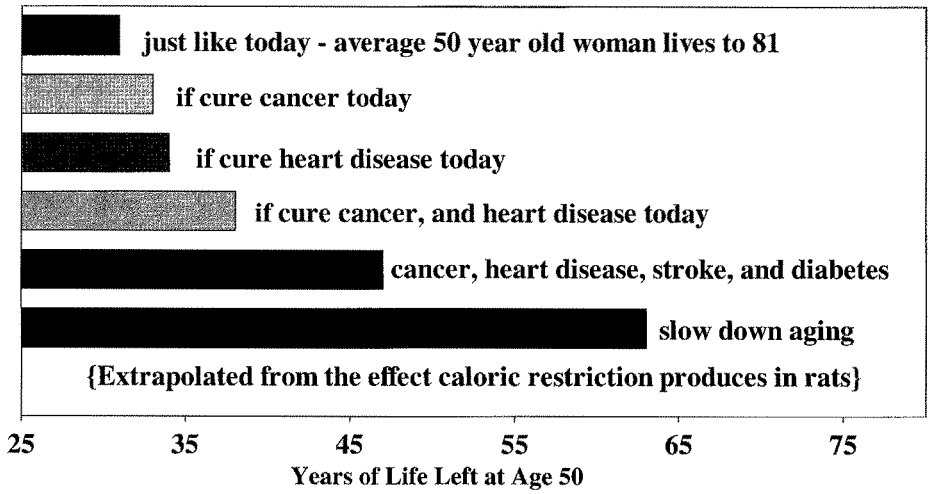

Figure 1. Calculated impact of various biomedical advances on human life span. The bars show the estimated extension of human life span, if various age-related diseases were cured **today**, compared to life span extension extrapolated from the effect of caloric restriction in rodents. These calculations are adapted from Olshansky *et al.* (1990).

THE GROWTH HORMONE PARADOX

A serious concern in the search for interventions that increase life expectancy is that interventions having short-term benefits could have adverse effects with long-term treatment. An excellent example of this is growth hormone (GH). It has been well documented that circulating levels of growth hormone drop with increasing age (Finkelstein et al., 1972; Rudman et al., 1981; Printz et al., 1983). It has also been shown that GH replacement in adults with pituitary disease and GH deficiency has beneficial effects on body composition, reducing fat and increasing lean body mass, muscle strength, and bone mass (Gibney et al., 1999; Johansson et al., 1997; Johansson et al., 1999; Amato et al., 1996). Daniel Rudman et al. (1990) investigated whether growth hormone injections into older men would restore muscle mass typical of younger men. They injected growth hormone three times a week into 12 men over a period of six months, and looked for changes in body composition and IGF-I levels. They found that IGF-I levels did rise and that lean body mass increased, while fat mass decreased, suggesting that growth hormone injections did reverse the changes in body composition that were due to age and deconditioning. This report encouraged the use of growth hormone as an anti-aging intervention.

However, more recent data obtained with mice suggest the opposite conclusion. Lifelong over-production of growth hormone shortens longevity in mice (Wolf et al., 1993), while under-production or an inability to respond to growth hormone lengthens it (Coschigano et al., 2000; Bartke et al., 2001). Transgenic mice over-expressing growth hormone exhibit severe kidney lesions and increased incidence of neoplasms, while over-production of growth hormone in adult humans leads to a condition known as acromegaly, which is characterized by excessive growth of certain organs and tissues (especially bone), but also premature heart and lung failure. Thus, efforts to restore circulating growth hormone to youthful levels in older individuals may be misguided. Furthermore, the evidence from both nematodes and fruit flies suggests that decreased activity of the growth hormone/insulin-signaling pathway is associated with increased life expectancy, rather than the reverse. Further research is needed before growth hormone supplementation in humans can be considered either safe or useful for long-term intervention.There is an important caveat with regard to injection of growth hormone, in that it does not replicate the normal pulsatile pattern of growth hormone production seen in humans. A very low baseline level characterizes this pattern, with intermittent low amplitude peaks during waking hours and much larger peaks during periods of deep sleep. An alternative approach of using growth hormone releasing hormone (GHRH) has been tried, but with limited success. Somewhat better success has been obtained using a variety of GHRH and growth hormone releasing peptide mimetics, such as small peptides and aromatic ring compounds (summarized by Wolfe, 1998). In his conclusion, Jason Wolfe states: "... it is premature to conclude that GH reverses aging, just as it is premature to conclude that it does not."

TELOMERASE AND TELOMERES

Telomeres are the non-coding, repetitive sequences at the ends of chromosomes. It is now known that telomere shortening is in some way linked to cessation of cell proliferation (also referred to as replicative senescence) in human cells (Warner and Hodes, 2000). Telomeres shorten each time a cell divides, and the original telomere length cannot be maintained because most human cells lack the enzyme telomerase. Exceptions to this are germline cells, lymphocytes, and probably stem cells and cancer

cells. Thus, the average telomere length in a population of cells in a proliferative tissue, such as skin and liver, gradually decreases with increasing age. Once telomeres reach some critical length, cell division stops. Although very few of these senescent cells actually accumulate with age in human tissues (Dimri et al., 1995; Severino et al., 2000), some gerontologists have proposed that replicative senescence, and/or the telomere shortening that may cause it, might nonetheless be important factors in life expectancy determination in humans (reviewed by Banks and Fossel, 1997; Fossel, 1998; Fossel, 2000).

The discovery that inserting and expressing the human gene for telomerase in human fibroblast and retinal pigment epithelial cells markedly increases the proliferative potential of these cells (Bodnar et al., 1998), led to some undeserved optimism about future mortality rates. As John
10 Wilmoth (1998) put it: "Recently, the manipulation of a gene that halts the shortening of telomeres during the replication of human cells *in vitro* was a source of great optimism in the popular media, provoking rather extraordinary claims about the possibility of surviving to unprecedented ages in the near future." The current reality is that there is at present no convincing evidence that "running out of cell divisions" actually contributes to aging of the organism. While there are theoretical reasons for believing that there may be some tissues in which proliferative failure contributes to the declining physiology associated with aging, those tissues have yet to be unequivocally identified. Experiments with mice deficient in telomerase activity have shown that the absence of telomerase does lead to premature pathology in the form of increased skin lesions and genetic instability, and decreased resistance to stress (Rudolf et al., 1999). However, because most mouse cells normally contain telomerase activity and most human cells do not, Shay and Wright (2001) point out that understanding this difference "will be essential for designing and interpreting experiments that investigate how replicative senescence, telomeres and telomerase are involved in aging and cancer."

Premature telomere-based replicative aging occurs in cells from patients with premature aging syndromes such as Werner's Syndrome and progeria. This observation suggests that replicative senescence, possibly as a result of increased cell turnover due to the primary molecular defect, may contribute to some of the human aging phenotypes that are seen in these patients and in normal aging. The advances in our understanding of the evolutionary forces that produce aging strongly argue that replicative aging of cells would be only one of many different processes that contribute to aging. While it is an important area of research to pursue, there is insufficient basis at present for claiming that preventing telomere shortening would influence any aspect of aging. Telomerase deficiency in humans does lead to premature skin lesions (Mitchell et al., 1999), but this does not mean that patients with dyskeratosis congenita are aging prematurely.

STEM CELLS AND CELL REPLACEMENT THERAPY

The genetic manipulations summarized in Table 1 appear to have little potential for direct application in humans, although they do provide insight into important biological factors in longevity determination in model systems. In contrast, the potential of cell replacement therapy in reversing some of the adverse effects of aging appears to be substantial. Aging is accompanied by some loss of tissue function, at least partially due either to the age-related loss of cells from the tissue, or to an increased proportion of dysfunctional cells. One example is the loss of specific types of neurons, which causes a variety of neurodegenerative diseases such as Parkinson's disease, Alzheimer's

disease, and amyotrophic lateral sclerosis. Until the causes of this neuronal loss can be identified and prevented, cell replacement appears to be a theoretical alternative. Fred Gage has recently reviewed the current status of, and the potential for, use of stem cells for cell replacement therapy in the central nervous system (Gage, 2000). Preliminary results using fetal stem cells to restore function to paralyzed rat limbs have been recently reported (Vogel, 2001a).

Several recently published reports demonstrate the potential of this strategy using adult stem cells. Helen Blau and her colleagues (Brazelton et al., 2000) showed that adult mouse bone marrow cells could be used to repopulate neuronal phenotypic cells in the brain. Piero Anversa and his colleagues (Orlic et al., 2001) have reported comparable results with heart tissue. They showed that mouse bone marrow cells could be injected into myocardium near an infarcted area, and regenerate myocardium. Both groups used transgenic mice expressing green fluorescent protein to confirm the survival of donor cells and their descendents in the recipient tissue. These studies suggest the potential value of cell replacement therapy in restoring function to these post-mitotic tissues, thus ameliorating the debilitating effects of strokes, heart attacks and various neurodegenerative diseases.

The recent isolation of nearly totipotent cells such as the human embryonic stem (ES) cells offers an even greater range of opportunities (Thomson et al., 1998). These cells express telomerase and appear to maintain an immortal phenotype even over extended culture *in vitro*. Cells and tissues derived from such cultures may therefore provide the unique advantage of possessing a large replicative capacity. In addition, virtually any somatic cell type may theoretically be derived from the cells, even cells en route to terminal differentiation. An example of the utility of this approach is that myocardial precursors derived from mouse ES cells appear to graft into mature myocardium, apparently forming gap junctions with the neighboring myocardial cells and beating in synchrony (Klug et al., 1996). Such strategies for transplantation in the heart may eventually lead to novel therapies for arrhythmias, and even the restoration of heart function following ischemia or heart failure. More significantly, the replicative immortality and undifferentiated state of human ES cells may lead to targeted genetic modifications and subsequent differentiation into many medically-relevant cell types.

However, it is important to note that formidable hurdles are yet to be overcome (Rosenthal, 2001). First, cells derived from established human ES cell lines will probably not prove to be immunologically compatible with most patients. This may be resolved by immunosuppressive therapy, genetic modification of the cells to reduce immunogenicity, or possibly by creating a chimeric immune system in the patient to induce tolerance. The recent discovery of cell reprogramming through nuclear transfer offers a path to the reprogramming of a patient's cell, thereby reverting it to an autologous ES cell (Lanza et al., 1999). This approach has the advantage that immunocompatibility would likely result. In addition, telomeres are reconstructed in the process (Lanza et al., 2000a). However, the ethics of ES technology and the use of nuclear transfer in medicine are currently a matter of intense national debate (Lanza et al., 2000b), and implementation of the technology may be slowed by limitations imposed on NIH funding for stem cell research. Finally, it remains to be seen whether such new tissue (even if it were autologous) would be adequately vascularized and subsequently function appropriately in the patient.

An alternative approach to cell replacement therapy might be to insert the telomerase gene into

viable cells from the patient's own tissue. Such cells would then have the potential to undergo proliferative expansion, but would not be rejected by the recipient's immune system. Funk et al. (2000) have demonstrated the possible therapeutic use of such immortalized cells in a reconstituted human skin model.

HOW TO TEST POTENTIAL INTERVENTIONS

Based on caloric restriction and genetic intervention results with animal models, one can now make a principled argument that further research along well-defined lines could produce a rational, testable strategy for interventions that might slow aging and/or decrease vulnerability to age-associated diseases in people. Papers identifying interventions that may extend life expectancy and health span appear sporadically in the gerontological literature. Recent examples include
12 interventions in animals not only to reduce oxidative stress (Carney et al., 1991), but also to extend life expectancy with α-phenyl-N-tert-butylnitrone (Edamatsu et al., 1995; Saito et al., 1998); to restore biochemical and physical function with acetyl-L-carnitine (Hagen et al., 1998); to prevent cardiovascular and renal pathology with aminoguanidine (Li et al., 1996); and to extend life expectancy with melatonin (Pierpaoli and Regelson, 1994).

Unfortunately, one or more design flaws compromise many of these reports. For example, there may have been too few animals per cohort, failure to control for possible caloric restriction, use of an inappropriate animal model, or poor management. Furthermore, some research laboratories do not have either the resources or the expertise to design and conduct a scientifically robust study. For example, few of these studies have been accompanied by pathology or other biomarker assessment, which would help assess the impact of the intervention on health span. Because most of the informative endpoints in such a study may require invasive procedures, adequate testing cannot usually be done directly in humans. However, the identification of effective substances or treatments in an animal model could serve as a powerful spur and guide for the design of intervention studies in humans or non-human primates. A successful program to test interventions would achieve the above-stated goal and might also provide new theories and hypotheses about basic mechanisms of aging for further research. Finally, negative results could prevent continued investment of funds into unpromising areas of research.

A program of this kind would most likely be successful if it could bring together a group of experienced investigators to design a protocol for evaluation of interventions that reflects substantial consensus within the research community, and at the same time builds in standardization and replicability. Such a program would require the selection of an appropriate test animal model (or models), appropriate endpoints, and a strategy for selecting which compounds to test. Endpoints should be as non-invasive as possible, and should include survival analysis, pathology assessment, physiological function, cognitive function, growth rate, and biomarkers of resistance to various stresses (such as oxidative stress or heat). The mouse would appear to be the prime choice for a mammalian model, but the nematode, *Caenorhabditis elegans,* might be useful in a large-scale, but relatively inexpensive, screening program to identify possible intervention candidates for further testing in mice. The National Institute on Aging is currently considering development of such an intervention-testing program (Warner et al., 2000).

POLICY IMPLICATIONS

The adjective "anti-aging" has often been used to refer to both basic and clinical studies in this research area. A publication entitled *Journal of Anti-Aging Medicine* was established in 1998, and it currently publishes four issues per year. A society not related to the journal, called the American Academy of Anti-Aging Medicine, or A4M, was established in the mid-1990s to promote "anti-aging" medicine as a new and unique branch of medicine. Unfortunately, early claims for anti-aging interventions have often been supported by flimsy and anecdotal evidence. Applications have been based on such overly simplistic concepts as restoration of circulating hormones to youthful levels (see "The Growth Hormone Paradox," above). As a result, anti-aging has acquired a tarnished image in the gerontological community. Thus, the participants at this workshop discussed the use of an alternative name for this area, and settled on Longevity Science and Medicine. While the question of the best name for this research area remains open for debate, the participants concurred on the need to provide robust, long-term funding for it.

We believe "longevity medicine" should apply to all means that would extend healthy life, including health promotion, disease prevention, diet, exercise, cessation of tobacco use, as well as advanced medical care and new discoveries as a result of basic research.

As public awareness of aging research increases, (largely as a result of research advances funded by the National Institute on Aging and several private foundations, and the advocacy of "anti-aging" medicine by organizations such as A^{4}M), the Food and Drug Administration (FDA) has acknowledged the possible need to regulate drugs claiming anti-aging benefits. Unfortunately, there are no unequivocal biomarkers of aging that could be used to rigorously test longevity-promoting interventions using mice or rats in pre-clinical trials. Thus, it may be difficult for the FDA to establish rigorous criteria to facilitate testing of putative interventions. However, the National Institutes of Health recently established the National Center for Complementary and Alternative Medicine (NCCAM). This Center has a mandate to facilitate research on non-traditional medical approaches to prevent and treat disease and other pathology. Thus, it is anticipated that NCCAM may become increasingly involved in funding clinical trials of at least some putative longevity-promoting interventions, and the FDA will have the opportunity to monitor safety and efficacy. Finally, an important political issue is whether U.S. government-funded research with human stem cells will be limited to use of adult stem cells, or whether embryonic stem cells will become available in the near future. At the time of publication of this report, the question has been partially resolved. The position of the National Institutes of Health as of August 23, 2000, was that embryonic stem research could be supported, provided that U.S. government funds were not used to derive the embryonic stem cells (http://www.nih.gov/news/stemcell/stemfactsheet.htm). On August 9, 2001, the Bush administration decided that research using human embryonic stem cells could proceed with federal funding, but using only the stem cell lines already available. Meanwhile, the scientific debate continues about what kind of stem cells and how many cell lines will suffice (Vogel, 2001b).

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Public Information

The American public is bombarded with advertisements for, and books about, products that will restore youthful appearance and function. These products include anti-oxidants (to neutralize oxygen free radicals); chelators (to bind heavy metal ions such as copper and iron); DHEA (to rejuvenate the immune system, improve brain

function, relieve stress, etc.); growth hormone (to increase muscle mass and function); and retinoic acid (to decrease skin wrinkling). Although each of these interventions is at least distantly related to some experimental observation, the public must be warned that the vast majority of these interventions have not been adequately tested for safety, and there is little or no evidence of efficacy in human clinical trials. It is equally important for the public to be aware that most of us already have access to inexpensive behavioral interventions that have been demonstrated to extend length and improve quality of life. They include exercise, a healthy diet, cessation of smoking, and moderation in use of alcohol.

The Public Information Office at the NIA routinely provides information to the public in the form of "Age Pages", which address a variety of health-related issues of interest to older individuals. These can be found at the website www.nih.gov/nia. A few examples particularly relevant to this workshop include:

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"Pills, patches and shots:
Can hormones prevent aging?"

"Life extension:
Science fact or science fiction?"

"Exercise: Feeling fit for life"

"Ginkgo biloba"

Further information about the following International Longevity Center-USA/Canyon Ranch publications can be obtained at www.ilcusa.org.

Prescription for Longevity: Fads and Reality

*Maintaining Healthy Lifestyles:
A Lifetime of Choices*

Achieving and Maintaining Cognitive Vitality with Aging

*Biomarkers of Aging:
From Primitive Organisms to Man*

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Glossary

ACETYL-L-CARNITINE – a biochemical compound which declines with age. This compound facilitates the ability of mitochondria to produce biochemical energy in the form of ATP.

ACROMEGALY – a disorder marked by progressive enlargement of bones; usually caused by over-production of growth hormone due to pituitary cancer.

ALZHEIMER'S DISEASE – an aging-dependent disease characterized by loss of memory. Risk factors include both genetic and environmental factors. Age of onset varies from the late 40s for patients with early-onset genetic risk factors, to 65 and older for most other patients.

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AMINOGUANIDINE – a compound used to reduce non-enzymatic glycosylation of proteins.

AMYOTROPHIC LATERAL SCLEROSIS – an age-related neurodegenerative disease caused by premature death of motor neurons; also known as Lou Gehrig's disease.

ANTIOXIDANT – a compound and/or enzyme that neutralizes reactive oxygen species, thereby reducing oxidative stress.

AUTOLOGOUS – pertaining to a tissue or structure occurring naturally and derived from the same individual.

BIOMARKER (OF AGING) – an age-related change which reflects the physiological age of an individual, in contrast to the individual's chronological age.

CALORIC RESTRICTION – a diet strategy to limit the caloric intake, while supplying all other essential dietary ingredients. This extends life expectancy and delays the onset of age-related disease in rodents.

CATALASE – an antioxidant enzyme that destroys hydrogen peroxide, converting it to water and oxygen.

CENTENARIAN – a person who has lived for at least 100 years.

CHELATORS – compounds that tightly bind metal ions, thereby preventing their normal chemical activity.

daf – a symbol for nematode mutants with developmental defects.

DEHYDROEPIANDROSTERONE (DHEA) – a circulating adrenal steroid hormone that has been widely promoted as an "anti-aging" hormone. Circulating levels decrease with age.

DYSKERATOSIS CONGENITA – a congenital condition characterized by defects in highly proliferative tissues such as skin and bone marrow.

EMBRYONIC STEM CELL – a stem cell obtained from an embryo (see STEM CELL, below). An embryonic stem cell is assumed to have the potential to differentiate into any kind of cell, and therefore be the most versatile in cell replacement therapy.

ESTROGEN – the major female hormone, produced primarily in the ovaries.

FIBROBLAST – one of the major cell types found in human skin. Fibroblasts have been developed as a model system for studying cellular aging.

GERMLINE – cells destined to become either eggs or sperm cells.

GREEN FLUORESCENT PROTEIN (GFP) – a specific protein that fluoresces green. The gene for this protein is used as a "reporter" transgene because the presence of GFP is easy to detect in tissues.

GROWTH HORMONE – a hormone produced in the pituitary that is essential for normal growth. Circulating levels decrease with age, and growth hormone replacement has been promoted as a possible anti-aging intervention.

GROWTH HORMONE RELEASING HORMONE – a hormone that directs the pituitary gland to produce growth hormone.

HORMONE – a substance produced in one tissue, but usually acting on another.

INSULIN-LIKE GROWTH FACTOR I (IGF-1) – a factor that resembles insulin and stimulates cell growth.

LIFE EXPECTANCY – the average length of life of a population of individuals.

LIFE SPAN – the maximum life span defines the age of death of the longest-lived member of a population.

LYMPHOCYTES – white blood cells involved in producing an immune response.

MELATONIN – a hormone produced in the pineal gland, which has a role in the sleep/wake cycle. Melatonin supplementation has been promoted as a possible anti-aging intervention.

MORBIDITY – the relative incidence of disease.

MORTALITY – the relative incidence of death.

MYOCARDIUM – heart tissue.

NEMATODE – a small worm, usually soil dwelling, which has been developed for biomedical research because of its well characterized developmental program. It is a useful model system for studying aging because of its short life expectancy.

NUCLEAR TRANSFER – the transfer of a nucleus from one cell into another cell lacking a nucleus.

OSTEOPOROSIS – a condition characterized by decreasing bone density with age, thus increasing the risk of bone fracture.

OXIDATIVE STRESS – the process whereby cellular macromolecules are damaged by reactive oxygen species, produced mainly in the mitochondria, leading to dysfunction.

PARKINSON'S DISEASE – an age-related neurodegenerative disease caused by premature death of neurons in the substantia nigra; characterized by rhythmic muscular tremors.

PITUITARY – a gland in the brain that produces several hormones, including growth hormone.

POST-MITOTIC TISSUE – tissues in which few, if any, cells are capable of replicating, such as tissues in the brain.

REPLICATIVE SENESCENCE – a condition characterized by the loss of proliferative capacity in individual cells. Telomere shortening is one cause of this.

RETINAL PIGMENT EPITHELIAL CELLS – pigmented cells found in the retina. These cells are essential for vision.

RETINOIC ACID – a compound that stimulates cells to differentiate into specific cell types.

STEM CELL – a special kind of cell that divides asymmetrically, in the sense that it appears to have the ability to continue to produce daughter cells without undergoing replicative senescence.

SUPEROXIDE DISMUTASE (SOD) – an antioxidant enzyme that converts the superoxide anion to hydrogen peroxide.

TELOMERASE – an enzyme that synthesizes telomeric DNA (see TELOMERE).

TELOMERE – the non-coding DNA at the ends of chromosomes, consisting of long stretches of short, repetitive DNA sequences.

TESTOSTERONE – the major male hormone, produced primarily in the testes.

TRANSGENE – a gene from one organism inserted into another. A mouse carrying such a gene is referred to as a transgenic mouse.

WERNER'S SYNDROME – a syndrome characterized by premature aging, usually starting in the twenties.

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The organization is part of a multinational research and education consortium, which includes centers in the U.S., Japan, Great Britain, France and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

Workshop Report

Biomarkers of Aging: From Primitive Organisms to Man

An Interdisciplinary Workshop of the
INTERNATIONAL LONGEVITY CENTER–USA

Sponsored by
The Ellison Medical Research Foundation
Kronos Longevity Research Institute
Institute for the Study of Aging
Canyon Ranch Health Resort

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Preface

By Robert N. Butler, M.D. and Richard L. Sprott, Ph.D.

The International Longevity Center and The Ellison Medical Foundation, joined by the Kronos Longevity Research Institute and the Institute for the Study of Aging, developed a workshop at Canyon Ranch Health Resort, where we assembled some of America's leading biologists and clinicians interested in aging to consider what we presently know about putative biomarkers of aging from rodents to man. Our goals were to come to a consensus, construct an agenda for future research, and make appropriate recommendations to policy-makers and the public-at-large.

These efforts are extremely important because of well-publicized claims that the means exist to directly intervene in aging processes. Obviously, to verify such claims and test interventions experimentally it will be necessary to have proven indicators which can monitor the aging processes, just as pressure readings are used to monitor cardiovascular health.

These considerations follow a significant scientific heritage which has resulted in an attempt to separate the normative, multi-causal processes of aging from diseases and other factors. It is understood that chronological age remains the most valid, if imperfect, biomarker of aging, and that aging per se is a risk factor for a variety of diseases, largely the polygenic conditions of late life such as Alzheimer's disease, cancer and coronary heart disease.

However, it is self-evident that chronological age cannot be used as a biomarker in the sense described above, because any intervention that is successful in slowing the aging process will, by design, result in asynchrony between biological and chronological age.

These thoughts proved critical to the results of the workshop. The biologists attending were able to describe in extraordinary detail the failure as yet to find validated biomarkers of aging in either rodents or man. At the same time, the clinicians were able to identify disease markers, risk factors and functional measures that show dramatic correlations with longevity and quality of life.

Aging processes are manifest in the famous Gompertz Curve, described in 1825 by a London actuary, Benjamin Gompertz. It shows the rise in the "force of mortality" with the passage of time. This important observation demonstrates profoundly why it is necessary to provide major funding for studies at the molecular and cellular level so that we may better understand what within our bodies increasingly predisposes us to disease, disability and ultimately death as we grow older.

At the same time, at an accelerated pace in the last half century, we have learned about many factors that adversely affect health, longevity and quality of life. The ability to recognize disease markers, risk factors and measurable functional activities offers enormous power to the clinician.

Thus, the workshop report that follows is divided into two parts. First, the biology of aging and the studies of biomarkers are described. Reasons

are given why there is no validity to current claims that a person's "real age" can be measured, and it is emphasized that such services should not be marketed to the unwitting public.

The second part describes some varied disease markers, risk factors and functional measures which do offer useful information to clinicians, and can help people alter their lifestyles to maintain or improve their health. These measures are critical "wake-up calls" to promote health and avoid unnecessary illness. ■

Workshop Overview

INTRODUCTION

What biological changes take place as we age? Efforts by scientists to uncover the biomarkers of aging, that is, the normal phenomena of growing old, and to separate these inevitable physiologic changes from diseases and other factors have yielded tantalizing clues but few definitive answers. We know that there are age-related risk factors for a number of diseases of older life, such as Alzheimer's disease. However, we do not know if they are simply *by-products* of aging, or if they are an *essential component* of the aging processes. Nor do we know how long and how well physiological functions can be maintained with increasing age. Finally, to date we cannot separate genetics, lifestyles, the environment and other idiosyncratic factors from age-related functions that are universal.

The biological markers of diseases and factors that make individuals vulnerable to certain diseases will enable clinicians to develop interventions to increase life expectancy and/or enhance function in aging populations. Biological markers of aging are also extremely important because of well-publicized claims that the means exist to retard or reverse aging processes. Obviously, to verify such claims and test putative interventions experimentally it will be necessary to have proven indicators which can monitor aging processes.

The International Longevity Center and The Ellison Medical Foundation, joined by the Kronos Longevity Research Institute and the Institute for the Study of Aging, held a workshop at Canyon Ranch Health Resort and assembled some of America's leading biologists and clinicians interested in aging to consider the question of whether biomarkers can be identified and used to measure the physiological age of any individual within a population, given emerging information about aging and new technological advances. Our goals were to come to a consensus, construct an agenda for future research, and make appropriate recommendations to policy-makers and the public-at-large.

A Definition of Aging

Our workshop report begins with a working definition of aging. Caleb Finch[1] offers a good overall definition: "A nondescript colloquialism that can mean any change over time, whether during development, young adult life, or senescence. Aging changes may be good (acquisition of wisdom); of no consequence to vitality or mortality risk (male pattern baldness); or adverse (arteriosclerosis)".

This report, however, focuses only upon the adverse aspect of aging: the processes that progressively convert physiologically and cognitively fit healthy adults into less fit individuals with increasing vulnerability to injury, illness and death. We are particularly interested in the changes organisms undergo that adversely affect their vitality and functional health over most of the adult life span.

[1] Longevity, Senescence, and the Genome. Caleb E. Finch. Chicago: University of Chicago Press, 1990, 671.

The Force of Mortality

While aging per se is a risk factor for a variety of diseases, such as Alzheimer's disease, cancer and coronary heart disease, chronological age cannot be used as a biomarker in the sense described above, because any intervention that is successful in slowing the aging processes will, by design, result in asynchrony between biological and chronological age. The famous Gompertz Curve, described in 1825 by a London actuary, Benjamin Gompertz, shows the rise in the "force of mortality" with the passage of time, which is the manifestation of the underlying biology of aging.

Clinical Criteria for Biomarkers

In the absence of a more complete understanding of the mechanisms of aging, clinicians would like to have age-related biomarkers that have adequate predictive value to provide information to their patients. This information could help improve organ function throughout the life cycle, and reduce unnecessary morbidity and premature mortality. These biomarkers must be more than disease risk factors, and represent individual indicators of functional status. Clinicians prefer functional biomarkers that relate to health expectancy, and that

1. Predict physiological, cognitive and physical function in an age-coherent way, and do so better than chronological age;

2. Predict the years of remaining good function, and the trajectory toward organ-specific illness in the individual;

3. Are minimally invasive, and accessible to many individuals.

Several types of data could be utilized, including anthropometrical data, such as body mass index, body composition, and bone density; functional challenge tests, such as glucose tolerance test and forced vital capacity; and physiological tests, such as cholesterol/HDL.

These biomarkers could be measured in a large group of people who have reached an age where functional loss is known to occur most rapidly (i.e., the 60 to 70 age group), but it would also be useful to have data on younger adults as well. Analyses would help to identify tests whose predictions were most accurate when matched against actual functional outcome and morbidity patterns. Tests with the best predictive value would become functional biomarkers. They could be used to test specific clinical approaches and therapies that focus on improvement of physiological, cognitive and physical functioning and their relationship to functional age. The optimal goal would be to obtain functional biomarkers with which personalized medicine or other interventions could be developed, to effectively reduce morbidity and improve organ-specific function. Achieving this goal would delay the necessity for costly hospitalization or social support of the aging population.

Ongoing Research

A number of studies have advanced our knowledge, at the same time as they raise provocative questions:

- It is well-documented that growth hormone levels fall with increasing age. Does this mean that low growth hormone levels accelerate aging? Not necessarily. It is equally plausible that falling growth hormone levels may merely reflect other aging processes which lead to dysregulation of a variety of cells, including cells that secrete growth hormone and those that regulate their secretion. In fact, lower growth hormone levels may be an indicator of health. Research findings on mice that overproduce growth hormones indicate that they live only a short time, suggesting that growth hormone deficiency per se does not cause accelerated aging, but that the opposite may be true[2].

[2] Bartke A, Brown-Borg H, Mattison J, et al. 2001. Prolonged longevity of hypopituitary dwarf mice. Exp. Gerontol. 36: 21-28.

- In 1935, Clive McCay first reported the effects of aging and caloric restriction in rats and mice. Today, there is a body of literature which shows how caloric restriction alters age-related pathology [3,4].
- Research suggests that the nervous system is a critical factor in regulating the life span in laboratory worms (nematodes), and that mutations in a specific gene can result in dramatic life span extension[5]. We do not know if the nervous system of mammals is similarly implicated, and if so, how this occurs.
- Studies have shown that chromosomes become shorter each time a human cell divides, as their ends are removed and not replaced[6]. These end regions, known as telomeres, should at least be considered as a possible biomarker of human aging. While telomere length is an indicator of how many times a human cell has divided, rather than a direct indicator of aging per se, it can be an indicator of functional age in certain human cells or in tissues where replicative potential is crucial to function, such as fibroblast involvement in wound healing.
- Imaging techniques, including nuclear magnetic resonance (NMR) and positron emission tomography (PET), hold particular promise in overcoming some of the technical problems associated with studies of aging over extended periods of time (longitudinal studies). With the recent development of high-resolution cameras capable of imaging small animals, it is now possible to perform relatively non-invasive studies on rats and mice as they age. Functional NMR can be used to study the changes in anatomy and metabolic activity in the brain and other tissues during aging. PET imaging may be used to study the neurochemical changes that occur in the brain during aging, including changes in neurotransmitter receptors and neurotransmitter synthesis.

[3] Lipman RD, Dallal GE, and Bronson RT. 1999a. Lesion biomarkers of aging in B6C3F1 hybrid mice. J. Gerontol. 54A: B466-477.
[4] Lipman RD, Dallal GE, and Bronson RT. 1999b. Effects of genotype and diet on age-related lesions in *ad libitum* fed and calorie-restricted F344, BN and BNF3F1 rats. J. Gerontol. 54A: B478-491.

Hurdles to Establishing Biomarkers

There are several hurdles to establishing informative biomarkers. One is the biological variation between individuals, which makes generalizations difficult. Another is the overlapping of aging and disease processes. Other hurdles include our uncertainty about which age-related changes are benign and which are indicators of pathology; we do not have enough information to determine if there is a point at which a process begins to do damage to the organism, and if so, the point at which it occurs; we do not know when to distinguish critical from non-critical damage. Finally, and significantly, it is difficult to obtain funding for this research.

Policy Implications

Obtaining support for a biomarker research agenda presents serious problems. The research program which was supported for 10 years (1988 – 1998) by the NIA was accomplished through set-aside funds and use of an ad hoc review process. Review of applications for biomarker research by regular Center for Scientific Review peer review groups at the NIH is not likely to result in sufficient numbers of funded applications to make substantial progress in this area in the near future because their focus is on the underlying mechanisms of diseases. Research on bio-markers does not address this concern. Clearly, a non-traditional long term source of funding is required, possibly involving commercial or philanthropic sources of support. However, as long as the Food and Drug Administration has no program for evaluating putative anti-aging interventions, commercial organizations are unlikely to perceive sufficient pay-off for funding such aging research.

[5] Larsen PL, Albert PS, and Riddle DL. 1995. Genes that regulate both development and longevity in *Caenorhabditis elegans*. Genetics 139: 1567-1583.
[6] Harley CB, Futcher AB, and Greider CW. 1990. Telomeres shorten during ageing of human fibroblasts. Nature 345: 458-460.
[7] Shelton, D. "Dipping into the fountain of youth," *American Medical News*, December 4, 2000.

Public Education

Leadership of the American Academy of Anti-Aging Medicine and others in the USA would have us believe that aging is not inevitable, and that "immortality is within our grasp"[7]. They believe that well-validated biomarkers of aging already exist which can be used to evaluate individuals at a cost of several thousand dollars per person, and that these evaluations can then be used to design individualized anti-aging treatments. Unfortunately these treatments include some poorly validated interventions such as improving anti-oxidant status and hormone replacement therapies, (e.g., growth hormone, testosterone, dehydroepiandrosterone [DHEA], melatonin, etc.)

While it is seductive to believe that restoring hormone levels back to levels that are produced in young persons is a good thing, and although it is true that hormone replacement trials have yielded some positive short term results, it is clear that negative side effects also may occur, in the form of increased risk for cancer, cardiovascular disease, behavior changes, etc. Estrogen replacement therapy in women has shown definite benefits, especially for prevention of osteoporotic fractures. Nonetheless, research on this hormone is still underway, and some recent studies have raised "red flags" with regard to the usefulness of estrogen for treating or preventing coronary heart disease. The risk/benefit ratios for testosterone replacement and growth hormone treatment have not been established in older persons. Finally, trials of DHEA have failed to show significant clinical benefits in normal aging. Clinical trials to investigate the risks and benefits of these and other potential interventions are either still going on, or have not yet provided definitive answers. The public is advised to exercise caution in requesting these popular anti-aging interventions until adequate clinical trials have been completed and analyzed.

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[7] Shelton, D. "Dipping into the fountain of youth," *American Medical News*, December 4, 2000.

The participants of this workshop strongly recommended continuing research on these and other hormones, antioxidants and agents that may have favorable effects upon the promotion of health, e.g., the possibility that some anabolic hormones protect, if only for a short term, against the frailties of old age. At the same time, advancement of healthier lifestyles with attention to diet, exercise, tobacco cessation and early identification of risk factors, measurements of functional status and disease markers are desirable and achievable goals. For example, it is important to lower cholesterol levels through exercise or the use of pharmacological agents like statins, and to detect hypertension and diabetes early in order to effect appropriate control and prevent the often lethal consequences of both.

Conclusion

Early identification of risk factors, measurements of functional status and disease markers are desirable and achievable goals, and new studies are advancing our understanding of factors that contribute to health and longevity, among them exercise, smoking cessation, nutrition, environmental and genetic factors. At the same time, our rapidly aging population increases the relevance of research to find age-related biomarkers. Although a definitive panel of biomarkers for assessing physiological age of individuals within a population has not yet been achieved, studies using organisms in the laboratory continue to provide researchers with important data. The ultimate goal is to develop age-related biomarkers to measure interventions that may increase life expectancy and enhance healthy aging for as long as possible. ■

The Workshop Report

INTRODUCTION

A discussion about biomarkers of aging immediately runs into some difficulty, first because few people can agree on a definition of aging, and second, because different definitions of "biomarker" are employed by basic and clinical scientists with different interests and backgrounds. Edward Masoro pointed this out in 1988 when he wrote that "there are two major reasons why there is controversy about the use of physiological systems as biomarkers of aging: one relates to the lack of knowledge about the basic aging processes and the other is the confusion about what a biomarker of aging is designed to do" (Masoro, 1988). Leaving aside for the moment the question as to whether such barriers to biomarker development are insurmountable, we must begin with a working definition of aging. One good overall definition is that aging is "A nondescript colloquialism that can mean any change over time, whether during development, young adult life, or senescence. Aging changes may be good (acquisition of wisdom); of no consequence to vitality or mortality risk (male pattern baldness); or adverse (arteriosclerosis)" (Finch, 1990). For the purposes of this discussion however, we will focus upon the adverse aspect of aging: the process that progressively converts physiologically and cognitively fit healthy adults into less fit individuals with increasing vulnerability to injury, illness and death. We are particularly interested in the changes in an organism that adversely affect its vitality and functions over most of the adult life span.

At the workshop, biomarkers of aging were defined by participant Richard Miller as traits which meet three criteria:

1. The biomarker should predict the outcome of a wide range of age-sensitive tests in multiple physiological and behavioral domains, in an age-coherent way, and do so better than chronological age;
2. It should predict remaining longevity at an age at which 90% of the population is still alive, and do so for most of the specific illnesses that afflict the species under study;
3. Its measurement should not alter life expectancy or the outcome of subsequent tests of other age-sensitive tests.

This definition provided a framework for the discussion at the workshop.

The second criterion implies that biomarkers are likely to be measuring degenerative processes, not just age-related change. Some effects of age, such as experience and judgment, may be beneficial, but are unlikely to pass the second criterion. Others, such as gray hair or skin wrinkles, may themselves have little effect on mortality risks, yet still serve as easily measurable indices of underlying degenerative processes that do increase vulnerability.

A continuing controversy is whether there exist processes of aging per se, which can be identified and studied independently of age-related disease. It is clear that there are age-related risk factors for

disease, and that these overlap with risk factors for aging, but there is disagreement about whether diseases to which older persons are vulnerable should be considered merely by-products of aging, or an essential component of the aging processes. This seems to be primarily a semantic issue for some, but a major question for others, and the issue cannot be settled here. What is important is how long and how well physiological functions can be maintained with increasing age; whether and what measurements can be done to assess this biologically, and in so doing obtain a multi-component physiological yardstick for aging. Ultimately, the goal is to use this tool to develop interventions that increase life expectancy and/or enhance function in aging populations.

NIA-SPONSORED WORKSHOPS IN 1981 AND 1986, AND THE 1988-1998 BIOMARKERS INITIATIVE

This is at least the third workshop on Biomarkers of Aging. In 1981 the National Institute on Aging organized its first conference on nonlethal biological markers of physiological aging. A second workshop, also sponsored by the National Institute on Aging (NIA), was held in 1986 in Chicago, Ill. It was convened to discuss "strategies for the conduct of biomarkers of aging research prior to the initiation of a request for biomarker research applications by the National Institute on Aging. The intent of the NIA was to generate interest in biomarker research, update general understanding of the biomarker concept, and most important, solicit the advice of knowledgeable scientists before issuing requests for research applications in this area" (Sprott, 1988). Such a request for applications was issued by the NIA in 1987, and applications were funded beginning in Fiscal Year 1988. The program was renewed for five more years in 1993, and continued until 1998. Although the research was done on genetically homogeneous strains of rats and mice, the hope was that any panel that was developed might also be relevant to human populations which are genetically heterogeneous.

This 10-year initiative resulted in many publications, but it appears that a definitive panel of biomarkers for assessing the physiological age of individuals within a population was not achieved. A series of seven papers was published in the November and December, 1999 issues of the Journal of Gerontology (v.54A, p.B464-566). These reports are among the first to summarize the results of this broad initiative (Sprott, 1999). They include a comprehensive summary of the age-related pathology observed in the rats and mice used in this study and how caloric restriction alters it (Lipman et al., 1999a, 1999b), as well as an extensive characterization of growth and survival characteristics of the various mouse and rat models used (Turturro et al., 1999). The remaining four papers describe a variety of attempts to identify and/or validate various biomarkers of aging, such as age-related changes in the potential for cell proliferation (Wolf and Pendergrass, 1999), changes in circulating hormones (Sonntag et al., 1999) and brain MAPK signaling (Zhen et al., 1999), and behavioral changes (Markowska and Breckler, 1999). The work supported by this NIA biomarker initiative thus added to the literature documenting the effects of aging and caloric restriction on a variety of interesting traits, but did not produce convincing evidence that these candidate biomarkers, separately or in combination, provided information about the "physiological age" of the individual upon whom the measurements were done.

2000 WORKSHOP

The purpose of this most recent workshop was to re-visit the question of whether biomarkers of aging can be identified and used to measure physiological age of any individual within a

population, given emerging information about aging and new technological advances. The meeting was organized by Robert Butler and Richard Sprott, and the participants included several individuals involved in the 1988-1998 initiative (Richard Feuers, Michael Forster, William Sonntag, Norman Wolf), several gerontologists not involved in the initiative (Jeffrey Bland, Michael Hewitt, Gerald McClearn, Richard Miller, James Nelson, Arlan Richardson and Richard Weindruch), and several clinicians (Howard Fillit, Mitchell Harman, Mark Hyman, Kathleen Johnson and Evan Kligman).

Their discussions centered on the following issues:

- What are the hurdles to evaluating and validating biomarkers of aging?
- Is the central nervous system a pacemaker of aging?
- Development of a research agenda
- Identification of possible interventions that might alter aging and delay age-dependent pathology
- Overlap between "biomarkers of aging" and "indicators of functional status"
- Policy implications
- Public education

What are the hurdles to evaluating and validating biomarkers of aging?

There are several hurdles to establishing informative biomarkers. One is the inter-individual and measurement variations which could be large enough to obscure differences due to aging-related change. Another is the overlapping of aging and disease processes as sources of change. Other hurdles include our uncertainty about which age-related changes are benign and which are indicators of adverse events; our lack of information about whether there are damage thresholds which only have a significant effect once these thresholds are breached, and if so what these thresholds are; our need to distinguish critical damage from non-critical damage (e.g., mutations need not lead to amino acid changes in proteins, and not all oxidized side chains in proteins will have functional consequences). Finally, there is the practical hurdle of obtaining support for the research needed; grant applications, including proposals to identify and validate biomarkers are unlikely to be enthusiastically reviewed by the usual peer review process, because of the perceived non-mechanistic nature of such research.

Is the central nervous system a pacemaker of aging?

Several recent publications describing research on *Caenorhabditis elegans (C. elegans)* suggest that the nervous system is a critical factor in regulation of life span in nematodes. Mutations in the *daf-2* gene in nematodes can result in dramatic life span extension (Larsen et al., 1995). The *daf-2* gene codes for an insulin receptor-like protein (Kimura et al., 1997; Wolkow et al., 2000) recently showed that restoring *daf-2* function in the neurons alone was sufficient to specify wild type life span, whereas a similar intervention in muscle or intestine had no such effect. The nervous system in nematodes has also been implicated in life span regulation by Apfeld and Kenyon (1999), who showed that mutations blocking sensory signal transduction extend nematode life span. Ailion et al. (1999) showed that mutations in *unc-64* extend nematode life span, and that the site of action of *unc-64* is neuronal, and through the insulin receptor pathway. Finally, overexpression of human Cu/Zn superoxide dismutase (SOD-1)

in motor neurons in fruit flies also extends life span (Parkes et al., 1998). Thus, this series of findings clearly implicate the nervous system in life span regulation in these two invertebrate systems, but the question remains whether, and how, the mammalian nervous system might be similarly implicated.

In the search for meaningful biomarkers of aging, the mammalian neuroendocrine system presents a more confusing picture. One interesting place to look might be regulation of either growth hormone (GH) production or function, because it is well-documented that circulating GH levels fall with increasing age, which suggests that low GH levels might accelerate aging. However, it is equally likely that falling GH levels may merely reflect one or more underlying aging processes which lead to dysregulation of differentiated cells of various types, including those that secrete, and those that regulate the secretion of GH. Moreover, there are several lines of evidence that suggest that GH deficiency per se is not a cause of accelerated aging, and that the opposite may be true. These include the following: mice overproducing GH are short-lived (Bartke et al., 2001); mice selected for slow growth rates in the first two months of life are relatively long-lived (Miller et al., 2000); dwarf mutant mice (*df* and *dw* mutations) with defects in GH, prolactin, and thyroid stimulating hormone production, have extended longevity (Brown-Borg et al., 1996; Miller, 1999), as do GH receptor-deficient mice (Coschigano et al., 2000); and the inverse correlations between body size and life span in mice and dogs (Miller, 1999). These *df* and *dw* mice have defects in pituitary development, and as a result exhibit multiple endocrine deficiencies. It is not known which deficiency, if any, is critical for life span extension, but it is worth noting that GH receptor-deficient mice are neither thyroid nor prolactin-deficient.

One possible new tool for looking at age related changes in brain function is gene expression microarray technology. Lee et al. (2000) have reported a first experiment to investigate such changes in mouse cerebellum and neocortex using arrays representing 6,347 genes. Their general conclusion was that aging-related changes in these tissues are indicative of increased oxidative stress and an inflammatory response with increasing age. However, it is too early to know how useful microarrays will be in identifying informative transcriptional biomarkers of either brain function or aging, and if they are, which genes will be critical. Finally, the use of neuroimaging technologies is also promising for the development of brain-related biomarkers. Imaging techniques can be used to estimate changes in brain activity, and thus indirectly cell number. Significant reduction of cell number in brain, or other critical tissues, might predict physiological age and mortality. These new tools will be briefly addressed in the next section.

Development of a Research Agenda

The 1988-1998 NIA Biomarkers of Aging Initiative was based on the idea that biomarkers would be modulated by caloric restriction (CR) intervention. It still seems reasonable that at least some physiological indicators of aging may be so modulated, as CR remains the only known intervention to reliably retard aging and extend maximum life span in a wide variety of species (Masoro, 2000). Of some relevance is the recent observation that the expression of only about two per cent of mouse genes in post-mitotic tissues are changed by two-fold or more during aging in mice, and that many, but not all, of these age-related changes are reversed by CR (Lee et al., 1999; Lee et al., 2000). In fact, incomplete reversal of age-related changes in gene expression by CR may provide insights into which changes are critical in aging (Han et al., 2000).

If one assumes that genes whose expression changes with age are likely to be associated with informative biomarkers of aging, then it becomes important to ask what is the potential for gene expression microarray analysis in biomarker research using mice? Such an approach might require two stages (Miller et al., 2001). The first stage would be to test all known mouse genes for changes in expression greater than some arbitrary amount, say 50% or 100% change, using enough mice to achieve statistical significance. Further levels of complexity of such an undertaking are that, 1) many genes are expressed in a tissue-specific manner, so that multiple tissues would have to be examined separately; 2) it will be necessary to follow the sequence and patterns of changes over a range of ages, rather than to simply examine animals arbitrarily defined at two age points as young and old; and, 3) it will be necessary to examine changes in several strains of mice, because some apparent aging changes may turn out to be strain-specific. Although the complete sequence of the mouse genome is not yet known, the sequence is expected to become available in the next 2-3 years. As various DNA-based microarray technologies improve, there is optimism that changes of as little as 20% may be reliably detected (personal communication, Minoru Ko, Gerontology Research Center, Baltimore, MD). Once this has been done, the expression of all qualifying genes, that is, genes showing statistically significant age-related changes of at least some minimum magnitude in more than one strain, would need to be re-examined as a function of tissue and at a variety of ages, and these changes related to development of pathology, to identify which changes in gene expression might be informative. Unfortunately the invasive nature of such an experiment precludes its use in longitudinal studies for most tissues, so the remaining life span of the individual mouse could not be determined. However, cross sectional results should identify some small number of genes whose expression changes substantially enough with increasing age to be a putative biomarker of the condition of some physiologically important system(s).

Just how many genes will be identified in this way depends upon the sensitivity and reliability of the microarray system used, and the amount of biological variation inherent in the expression of each gene (Dozmorov et al., 2001). It will also depend on the percent change and statistical significance limits imposed in the first phase. The results of Lee et al. (1999, 2000) suggest that the theoretical maximum number of mouse genes would be no larger than about 1,000 genes for any given tissue, assuming there is a total of about 50,000 mouse genes and that both increases and decreases are relevant. Major caveats to this approach include the potential high variability among results obtained from genetically heterogeneous individuals; the possibility that highly relevant "age indicators" may lie below the detection limit in such an analysis; and the invasive sampling procedure required. Nevertheless, DNA-based microarray technology is potentially very powerful, and as the reliability and sensitivity of the technology improves, it should eventually become useful in evaluating the physiological status of aging animals and/or humans. Future development of protein-based microarray technologies for screening the amount and activity of specific proteins may turn out to provide an even better approach (MacBeath and Schreiber, 2000).

The caveats discussed above apply as well to the validation of any potential biomarker of aging. However, each type of potential biomarker will also present its own unique hurdles. There is no doubt that aging and age-related pathology are accompanied by oxidative damage, but it is less clear which oxidative modifications are critical. The presence of 8-hydroxyguanine in DNA and

amino acids with oxidized side chains in proteins are generally accepted biomarkers of oxidative stress, but it is not clear whether global measurements of oxidative stress are sufficiently informative to provide biomarkers of aging. Techniques for measuring levels of 8-hydroxyguanine in DNA are much improved over those used 5-10 years ago, but it is not yet clear how good an indicator of aging they may be. Pero et al. (2000) have suggested that as crude a measurement as serum protein sulfhydryl groups correlate with mammalian life span. A more promising approach might be to identify proteins which are essential for a critical function, such as ATP production, and may become rate-limiting through oxidative or other damage. Two examples of this are cis-aconitase (Yan et al., 1997), and adenine nucleotide translocase (Yan and Sohal, 1998). Two other candidates are glutamine synthetase (Carney et al., 1991), which detoxifies ammonia while lowering glutamate levels in the brain, and poly ADP-ribose polymerase (Pero et al., 2000), which is essential for DNA repair in eukaryotic systems.

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If aging is at least partially reflected in a loss of ability to maintain homeostasis, then a decrease in one or more stem cell populations might predict there is less life span remaining, especially if these stem cells are critical for replacement of cells lost through apoptosis. However, no direct evidence exists to suggest that this is so, and good methods for isolating and characterizing stem cells are not yet available. In a similar vein, some measure of DNA repair capacity might predict the ability to maintain genetic stability, and thus homeostasis. Although DNA damage is most frequently associated with cancer risk, a defective Werner's syndrome gene leads to genetic instability and some aspects of aging prematurely, as well as increased tumorigenesis (Oshima, 2000). The Werner's syndrome gene product may very well be involved in DNA repair as it codes for both DNA helicase and 3' exonuclease activities, and loss of these two activities appears to be related to premature aging.

Studies have shown that chromosomes become shorter each time a human cell divides, as their ends are removed and not replaced. (Harley et al., 1990) These end regions, known as telomeres, should at least be considered as a possible biomarker of human aging. While it is clear that telomere length is an indicator of how many times a human cell has undergone cell division rather than a direct indicator of aging per se, it might be informative as an indicator of functional age in certain human cells or tissues where replicative potential is crucial to function, e.g., fibroblast involvement in wound healing. However, because of their initially long telomere length, rodent cells appear not to rely on telomere length-induced replicative senescence to limit the number of cell divisions available (Shay and Wright, 2001). Thus, attempting to validate telomere length as a biomarker in rodent cells may not be useful in developing a human biomarker for aging. However, there are reports that telomere length does decrease and might be correlated with aging in some rat tissues (Jennings et al., 1999; Kajstura et al., 2000).

A major problem with the above suggestions is that most require some invasive sampling, and thus are likely to violate criterion number three. Non-invasive sampling and measurements are much more desirable, which would limit experimentation to blood samples, anthropometric measurements, imaging techniques, or possibly skin, muscle or fat biopsies. Another problem is that they depend on correct guesses about candidate biomarkers, which earlier experience suggests have only a limited chance of success. A real biomarker validation program could be constructed by encouraging a substantial number of laboratories (perhaps 10?) to measure

overlapping sets of 10-25 biochemical, physiological or psychological traits, depending on the expertise of the laboratory, in several hundred genetically heterogeneous mice at several ages, and coupling these measurements with data on survival and pathology assessment at death. These data should be provided in a form suitable for statistical analysis to identify significant correlations among age-sensitive traits, and predictive value for life span and a variety of age-related diseases. Pre-existing data sets like the Baltimore Longitudinal Study of Aging and the Framingham longitudinal studies should also be mined for analogous traits in humans. Also, genetic studies on centenarians may increasingly identify both favorable and unfavorable alleles for promoting long life (Perls et al., 2000; Perls, 2001). These combined approaches should identify some promising biomarkers to be validated prospectively in human studies.

Merely showing that a given assay changes with age, and thus distinguishes most old people from most young people, is not sufficient to qualify a test as a biomarker. There are, and will continue to be, many candidates for biomarkers, but the real challenge in developing a productive research agenda is to validate some of these as true biomarkers. The test in question must divide people (or mice) of a given age into groups that differ predictably in a wide range of other age-sensitive traits (Miller, 1997).

Imaging techniques, including nuclear magnetic resonance (NMR) and positron emission tomography (PET), hold particular promise in overcoming some of the technical problems associated with longitudinal studies of aging. With the recent development of high-resolution cameras capable of imaging small animals, it is now possible to perform relatively non-invasive studies on rats and mice as they age. Functional NMR can be used to study the changes in anatomy and metabolic activity in the brain and other tissues during aging. PET imaging may be used to study the neurochemical changes that occur in the brain during aging, including changes in neurotransmitter receptors and neurotransmitter synthesis. A drawback of these procedures in animal studies is the need to anesthetize the animals, and proximity to the necessary imaging facilities. An exciting new use for PET imaging is the non-invasive imaging of reporter gene expression in living animals (Herschman et al., 2000). Using PET reporter genes and PET reporter probes investigators can examine the transcriptional activity and activation of promoters incorporated in transgenes or in viral vectors. One enormous potential advantage of non-invasive imaging of gene expression in living animals is that repeated analysis of gene expression could be made during experimental manipulations. With the rapid advancements in this area, it is quite possible that imaging techniques will become available that will allow scientists to monitor non-invasively, in real time, the levels of reactive oxygen species in tissues and groups of cells. This technology is becoming extremely important in aging research, especially in studies with human subjects (Bookheimer et al., 2000; Small et al., 2000).

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Identification of Possible Interventions

One of the major reasons for identifying and validating biomarkers would be to obtain endpoints for testing possible interventions in a model system to retard, prevent, or even reverse adverse age-related changes, as discussed by Warner et al. (2000). These authors concluded that a comprehensive panel of informative endpoints in mice might include survival curves; pathology assessment; non-invasive endpoints such as locomotion, cognitive function, physiological function (e.g., T-lymphocyte subsets);

biomarkers of oxidative stress; other measures of resistance to stress; and gene expression microarray analysis. However, first these endpoints need to be validated as to their value as true biomarkers in such a testing program.

Although antioxidant interventions continue to be a favorite choice for testing, the success of such interventions has been mixed despite some epidemiological data suggesting that dietary vitamin E supplementation reduces the risk of heart disease in men and women (Rimm et al., 1993; Stampfer et al., 1993). Life span extension has been observed in invertebrate systems overexpressing Cu/Zn superoxide dismutase (SOD) (Parkes et al., 1998; Sun and Tower, 1999), but this is not a viable human intervention. However, Melov et al. (2000) have recently shown that a SOD/catalase mimetic called EUK-134, when added to the diet, does extend life span in nematodes, and using this compound in humans might be possible. In contrast, Richard Weindruch reported at the workshop that in his research laboratory no life span extension occurred in male middle-aged mice treated with a variety of compounds including a-lipoic acid, N-acetyl cysteine, vitamin E, coenzyme Q10, melatonin, and aminoguanidine, alone and in various combinations. However, these negative results do not preclude the possibility that some of these interventions might retard one or more organ-specific aging processes in either mice or humans.

A very recent paper suggests that genetically-induced reduction of the transport of dicarboxylic acids, key intermediates in the citric acid cycle, appears to slow aging in fruit flies (Rogina et al., 2000). This mutation could be mimicking one aspect of caloric restriction, which could possibly also be accomplished pharmacologically by using an inhibitor of this dicarboxylic acid transport enzyme.

It is widely accepted that mitochondria are the chief source of reactive oxygen species (ROS) in eukaryotic cells. Although it is not known exactly how much superoxide anion is generated by mitochondria during normal oxidative metabolism, estimates are in the range 1% - 5% of the total oxygen consumed by the electron transport system. This superoxide is converted to hydrogen peroxide by the mitochondrial Mn-superoxide dismutase. However, hydrogen peroxide itself is a reactive compound, and may leak into the cytoplasm, where it can peroxidize fatty acids in membranes or be converted to hydroxyl radical which rapidly damages proteins and nucleic acids. The enzyme catalase is necessary to convert this hydrogen peroxide into harmless oxygen and water. Also relevant is the discovery that cytochrome C leaking from damaged mitochondria is a triggering event for apoptosis (Green and Reed, 1998). This sequence of events is particularly damaging in post-mitotic tissue, where the potential for replacement of lost cells is extremely low. Thus, any intervention that can block this sequence of adverse events as close to the starting point as possible (i.e., the generation of superoxide anion by the electron transport system), should be considered a promising candidate to reduce age-related pathology and delay aging. An instructive line of research would be to elucidate how birds, with their very high metabolic rate, manage this potential oxidative stress problem (Holmes and Austad, 1995). Blocking apoptosis has also partially ameliorated pathological consequences in animal models of neurodegenerative disease and stroke (Friedlander et al., 1997; Kang et al., 2000), although apoptosis may also have positive roles during aging (Warner et al., 1997).

Overlap between biomarkers of aging and indicators of functional status

As defined earlier, biomarkers of aging can be interpreted to mean a parameter or set of parameters that define characteristics related to increasing mortality with chronological age. Another interpretation could relate to a set of parameters that define functional ability (i.e., physiological, cognitive and physical function), and its relationship to morbidity and mortality with chronological age. While the first definition seems best suited for establishing research approaches toward the understanding of the fundamental physiological and metabolic processes of aging, this second definition is applicable to the need of the clinician who manages patients requesting recommendations and/or therapies to reduce their morbidity and extend longevity. It is recognized that both definitions have value when applied in their respective settings, but are likely to converge with one another as the basic mechanisms of aging in humans become better established. It is reasonable to assume that real biomarkers of aging will also correlate with risks for multiple degenerative changes and functional decline in a variety of species.

In the absence of a more complete understanding of the mechanism of aging, clinicians would like to have age-related biomarkers that have adequate predictive value to provide qualified information to their patients to help improve organ-specific function throughout the life cycle, and reduce unnecessary morbidity and premature mortality. These biomarkers might be more than disease risk factors, and represent individual indicators of functional status. Clinicians might prefer a panel of functional biomarkers of aging that relate to health span. In concordance with Dr. Miller's criteria, these biomarkers should:

1. Predict physiological, cognitive and physical function in an age-coherent way, and do so better than chronological age.
2. Predict the years of remaining functionality, and the trajectory toward organ-specific illness in the individual.
3. Be minimally invasive, and accessible to many individuals.

There are several types of data that could constitute a panel of functional biomarkers of aging, including anthropometric data (body mass index, body composition, bone density, etc.), functional challenge tests (glucose tolerance test, forced vital capacity, etc.), physiological tests (cholesterol/HDL, glycosylated hemoglobin, homocysteine, etc.), genomic and proteomic tests.

Such a set of putative functional biomarkers of aging could be measured in a large group of adults who are at an age where functional loss is known to occur most rapidly, such as in the 60 to 70 age group, but it would also be useful to have data on younger adults as well. Statistical evaluation of the data using cluster analysis, pattern recognition, and principal component analysis would help to identify tests that had the greatest predictive value when matched against functional outcome and morbidity patterns. Those with the highest predictive value would be defined as functional biomarkers of aging. These parameters could then be used to test specific clinical approaches and therapies that focus on improvement of physiological, cognitive and physical functioning and their relationship to functional age. The optimal goal would be to obtain a panel of functional biomarkers of aging that could be used to develop personalized medicine or other interventions which effectively reduce morbidity and improve organ-specific function, thereby delaying the necessity for costly hospitalization or social support of the

aging population. At least one such attempt to do this has already been reported (Hochschild, 1990).

Policy implications

How can support be obtained for a biomarker research agenda? The research program supported for 10 years (1988-1998) by the NIA was accomplished through set-aside funds, and use of an ad hoc review process. Review of applications for biomarker research by regular Center for Scientific Review peer review groups at the NIH is not likely to result in enough funded applications to make substantial progress in this area in the near future because of the perceived non-mechanistic character of the research. Clearly, a non-traditional long term source of funding is required, possibly involving commercial or philanthropic sources of support. However, as long as the Food and Drug Administration has no program for evaluating putative anti-aging interventions, commercial organizations are unlikely to perceive sufficient pay off-for funding such aging research.

Some biomarker-relevant research is funded by NIA-funded centers, such as the Nathan Shock Centers, for example, in their gene expression microarray and animal model development cores, but none of these Centers has an overt commitment to biomarker research per se at this time. Moreover, research at these Centers remains more focused on basic mechanisms than on human physiology.

Public education

There are individuals and organizations in the USA who would have us believe that aging is not inevitable, and that "immortality is within our grasp" (Shelton, 2000). These same individuals believe there already exist well-validated biomarkers of aging which can be evaluated at a cost of several thousand dollars per person, and that these evaluations can then be used to design individualized anti-aging treatments. Unfortunately these treatments include some poorly validated interventions such as improving anti-oxidant status and hormone replacement therapies, including growth hormone, testosterone, dehydroepiandrosterone (DHEA), melatonin, etc. Although it is possible that by providing evidence of dysregulation of differentiated cell function, age-related hormonal changes may serve as useful markers of physiological aging, this has not been demonstrated experimentally for either humans or animals. While it is seductive to believe that restoration of hormone levels back to levels that exist in young persons should be a good thing, and although hormone replacement trials have yielded some positive results (at least in the short term), it is clear that negative side effects also may occur, in the form of increased risk for cancer, cardiovascular disease, behavior changes, etc. Estrogen replacement therapy in women has been shown to have definite benefits, especially for prevention of osteoporotic fractures, although some recent studies have raised "red flags" with regard to the usefulness of estrogen for treating or preventing coronary heart disease. The risk/benefit ratios for testosterone replacement and GH treatment have not been established in older persons. Finally, trials of DHEA have failed to show significant clinical benefits in normal aging. Clinical trials to investigate the risks and benefits of these and other potential interventions are either still going on, or have not yet provided definitive answers, and the public is advised to be cautious in requesting these popular anti-aging interventions until adequate clinical trials have been completed and analysed.

As important as reporting promising findings in biomarker research is demonstrating when popular "anti-aging" interventions have no effect, or worse, when they have adverse effects. The majority of participants in this workshop expressed concern about the use of human growth hormone, DHEA, melatonin, various antioxidants and other agents that are claimed to retard or reverse aging, especially given the fact that there are currently no valid biomarkers of human aging. On the other hand, the participants strongly recommended continuing research on these and other hormones, antioxidants and other agents that might have favorable effects upon the promotion of health (e.g., the possibility that some anabolic hormones might protect, if only for a short term, against the frailties of old age).

Concern was expressed over the Dietary Supplement and Health Education Act of 1994. It opened the doors to a multi-billion dollar health food store and Internet business that promotes a variety of agents that are claimed to retard aging and overcome age-related diseases. There is no FDA supervision even to assure the purity of substances offered for sale, let alone their effectiveness and dangers.

The concept of "anti-aging medicine" contrasts with modern gerontology which distinguishes between aging as natural phenomena and diseases, and the role of aging per se as a risk factor for diseases. Anti-aging medicine is not an established specialty although it is being hailed as such. Many lucrative medical practices have emerged which operate outside of the formal insurance system. Systems that suggest they have the ability to measure biomarkers of aging and that they possess the means to favorably affect them are not scientifically-based. These practitioners of anti-aging medicine should be distinguished from mainstream clinicians who are concerned with health promotion and disease prevention.

Nevertheless, advancement of more favorable lifestyles with attention to diet, exercise, tobacco cessation and early identification of risk factors, measurements of functional status and disease markers is a desirable and achievable goal. For example, it is important to lower cholesterol levels through exercise or the use of pharmacological agents like statins, and to detect hypertension and diabetes early in order to effect appropriate control and prevent the often lethal consequences of both. ■

Commentary and Acknowledgement

By Robert N. Butler, M.D. and Richard L. Sprott, Ph.D.

This publication is part of the Canyon Ranch Series, which focuses on bringing to public attention some of the significant ongoing work being done by researchers in a variety of fields to improve the health and longevity of individuals as they grow older. Maintaining Healthy Lifestyles discusses what social and behavioral scientists, and behavioral health experts have learned about helping people control the greatest risk factors facing Americans today: tobacco, a sedentary life and poor diet. Achieving Cognitive Vitality with Aging brings
12 yet another dimension to lifestyle modification, demonstrating that not only physical status, but also mental status is subject to modification.

It must be strongly emphasized that the claims of a "specialty" area of medicine known as "anti-aging medicine" are not rooted in academic medicine and science, and that anti-aging medicine is not a recognized specialty. Further, substances recommended by "anti-aging" doctors, such as DHEA and melatonin (n-acetyl-5-methoxytryptamine) have not been demonstrated to either significantly influence the health of older persons or to retard aging processes. Moreover, there can be dangerous side-effects. It should be understood that such notions are distinct from geriatric medicine, a growing and recognized field, designed to promote the health and treat the illnesses of older persons.

The concept of biomarkers remains an extremely important one. The effort to find nonlethal indicators of aging processes is well-defined in the criteria offered in the first part of this workshop report. Utilizing the methodology of caloric restriction in rodent and other animal models is one way to identify and validate such biomarkers if they exist and, indeed, eventually a complex panel of such biomarkers may provide increasing means of assaying the underlying critical age-related biological changes.

Because of the high association of aging with disease, and the importance of discovering biomarkers, additional support for research aimed at defining measures of the biological rate of aging should be made available beyond present funding levels at the National Institutes of Health. Indeed, hardly more than $100 million of the almost $18 billion in the NIH Fiscal Year 2000 budget was devoted to understanding basic processes that are relevant to late life disease, and even less is dedicated to understanding aging itself. While increasing amounts of money must go to understanding the genetic and environmental factors in health and disease, too little is devoted to research into the biological properties of aging.

The ILC-USA thanks Dr. Huber Warner for his remarkable efforts in preparing this report, and in re-creating the atmosphere and the healthy intellectual debate that characterized this extremely energizing workshop.

Thanks also goes to Nora O'Brien, M.A. for her assistance in coordinating the workshop and preparing this document, and to Judith Estrine for editing and supervising the publication of this workshop report.

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And finally, the man who is a walking symbol for the finest of healthy lifestyles, the ILC-USA pays special tribute to our Board member and founder of Canyon Ranch — Mel Zuckerman — whose generosity and inspiration made this Workshop possible. ■

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Glossary

Adenine Nuclotide Translocase – an enzyme required for transport of ATP from mitochondria to the cytoplasm.

Alzheimer's Disease – an aging-dependent disease characterized by loss of memory. Risk factors include both genetic and environmental factors. Age of onset varies from the late 40s for patients with early-onset genetic risk factors, to 65 and older for most other patients.

Aminoguanidine – a compound used to reduce non-enzymatic glycosylation of proteins.

Antioxidant – a compound and/or enzyme which neutralizes reactive oxygen species, thereby reducing oxidative stress.

Apoptosis – a genetically regulated program leading to cell suicide.

ATP – adenosine triphosphate, the major form of biological energy present in cells.

Biomarker (of Aging) – an age-related change which reflects the physiological age of an individual, in contrast to the chronological age.

Caloric Restriction – a diet strategy to limit the caloric intake, while supplying all other essential dietary ingredients. This extends life expectancy and delays the onset of age-related disease in rodents.

Caenorhabditis Elegans (C. elegans) – Latin name for species of nematode, a small soil-dwelling worm, which has been developed for biomedical research because of its well characterized developmental program; it is a useful model system for studying aging because of its short life span.

CIS-Aconitase – an enzyme involved in the citric acid cycle.

Citric Acid Cycle – a biochemical pathway found primarily in mitochondria, which provides energy for ATP synthesis.

Coenzyme Q – a component of the electron transport system in mitochondria.

Cytochrome C – a mitochondrial protein required for ATP synthesis; leakage of this protein into the cytoplasm induces apoptosis.

daf – a symbol for C. elegans mutants with developmental defects.

DNA Helicase – an enzyme which promotes separation of two complementary strands of DNA.

Dehydroepiandrosterone (DHEA) – a circulating adrenal steroid hormone which has been widely promoted as an "anti-aging" hormone; circulating levels decrease with age.

Eukaryotic – organisms whose DNA is present as chromosome pairs (includes all plants and animals).

Exonuclease – an enzyme which degrades DNA one nucleotide at a time; such enzymes are involved in DNA replication, repair, and recombination.

Glutamine Synthetase – an enzyme which combines ammonia with glutamate, both of which are neurotoxic, to form glutamine, which is non-toxic.

Growth Hormone – a hormone produced in the pituitary which is essential for normal growth; circulating levels decrease with age, and growth hormone replacement has been promoted as a possible "anti-aging" intervention.

8-Hydroxyguanine – one of many damaged bases found in DNA as a result of oxidative stress.

Life Expectancy – the average number of remaining years an individual can expect to live at any given age.

a-lipoic Acid – a simple organic molecule containing a sulfhydryl group; thus it is an antioxidant.

Longevity – the length of life of an individual, or the average length of life of a population of individuals.

MAPK – mitogen-activated protein kinase, a protein involved in signal transduction.

Maximum Life Span – the longest observed life span of an individual of any species.

Melatonin – a hormone produced in the pineal gland, which has a role in the sleep/wake cycle; the circulating level of melatonin decreases with age and melatonin replacement has been promoted as a possible "anti-aging" intervention.

Microarry Technology – technology permitting the assay of thousands of samples simultaneously without individual handling.

Mitochondria – an organelle within the cell where glucose and oxygen are metabolized to produce ATP, the main cellular source of biological energy.

N-acetyl Cysteine – a simple organic molecule containing a sulfhydryl group; thus it is an antioxidant.

Oxidative Stress – the process whereby cellular macromolecules are damaged by reactive oxygen species, produced mainly in the mitochondria, leading to dysfunction.

Pituitary – the gland which produces several hormones, including growth hormone.

Pply ADP-ribose Polymerase – an enzyme involved in DNA repair.

Prolactin – a hormone produced in the pituitary gland, acting primarily on the mammary gland to promote lactation.

Reporter Gene – a gene whose expression is easily measured, often because it produces a colored product.

Signal Transduction – the process of relaying a biological signal from one part of a cell to another.

Single Nucleotide Polymorphism (SNP) – a sequence difference in DNA found with relatively high frequency within a population.

Sulfhydryl Group – a sulfur-containing group with antioxidant properties found in some biological molecules.

Superoxide Dismutase (SOD) – an anti-oxidant enzyme which converts the superoxide anion to hydrogen peroxide.

T-lympocyte – a white blood cell produced by the thymus.

Thyroid Stimulating Hormone – a hormone produced in the pituitary gland which stimulates growth of the thyroid.

Transcription – the process of copying the sequence of DNA into messenger RNA.

Transgene – a gene from one organism inserted into another.

unc – a symbol for C. elegans mutants which appear to be "uncoordinated".

Werner's Syndrome – a genetic disease characterized by premature development of adverse age-related changes such as cataracts, cardiovascular disease, cancer; cataracts may develop as early as the 20s, with average age of death at 45-50 years.

The International Longevity Center–USA (ILC-USA) *is a not-for-profit, non-partisan research, education and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways and highlight older people's productivity and contributions to their families and society as a whole.*

The organization is part of a multinational research and education consortium, which includes centers in the U.S., Japan, Great Britain, France and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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The Institute for the Study of Aging, Inc., is a private, nonprofit foundation based in New York City. The Institute is one of the largest private sources of philanthropic funding for drug discovery and drug development in cognitive aging and Alzheimer's disease in the United States and internationally.

The mission of the Institute is to promote quality of life in old age. As cognitive impairment is the most significant threat to successful aging, the Institute's primary focus is to facilitate and promote the discovery and development of new therapies to treat the aging-related problems of cognitive decline and, specifically, Alzheimer's disease. Through the sponsorship of research conferences and workshops, the Institute is dedicated to finding ways to promote "cognitive vitality" with aging.

INTERNATIONAL LONGEVITY CENTER–USA

The International Longevity Center—USA is a not-for-profit, nonpartisan research, policy, and education organization whose mission is to help societies address the issues of population aging and longevity in positive and constructive ways and to highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research, policy, and education consortium with centers in the United States, Japan, Great Britain, France, and the Dominican Republic. These centers work both autonomously and collaboratively to study the impact of increased life expectancy and higher proportions of older people on nations around the world.

CANYON RANCH HEALTH RESORT

Canyon Ranch Health Resort, located in Tucson, Arizona and Lenox, Massachusetts sponsors workshops on nutrition, fitness, health, and longevity as part of a comprehensive approach to wellness. The resort offers a wide array of services provided by nutrition, fitness, medical, behavioral, and spiritual experts.

NATIONAL INSTITUTE ON AGING

In 1974, Congress established the National Institute on Aging (NIA), whose mission is to provide leadership in aging research, training, health information dissemination, and other programs relevant to aging and the elderly and, in doing so, to improve the health and well-being of older Americans. As one of the 25 institutes and centers of the National Institutes of Health, the NIA leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life.

The ideas, conclusions, and recommendations herein are solely those of the authors, the International Longevity Center, and the Institute for the Study of Aging and not those of the National Institute on Aging.

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All of the participants deserve special acknowledgement for contributing their passion and expertise to the discussions. Special thanks to Alan O'Connell for orchestrating the workshop from start to finish.

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Preface

Perhaps the greatest fear of old age is losing one's mind. Cognitive function affects a person's ability to interact and enjoy life. Loss of the mind may translate into an inability to even recognize one's loved ones. Fortunately, the results of recent clinical work and research insights are increasing our ability to influence mental health status in aging.

The "longevity revolution" has increased our focus on many aspects of health in aging, including cognitive health. Cognitive vitality in old age has become an increasingly important health care goal. Although many older individuals are enjoying optimal aging, a substantial number of them still face their later years with serious decrements in cognitive function. These decrements can significantly affect quality of life.[1] And when cognitive decline progresses to dementia, the problem becomes far more serious. Alzheimer's disease (AD), the most common cause of dementia, has a devastating impact on individuals and society.

Our focus on achieving cognitive vitality is a relatively new conceptual approach made possible by new knowledge gained during the past decades from research on cognitive aging and AD. Now, we more clearly understand the distinctions between normal cognitive aging and diseases of cognition in old age. Research has also resulted in many new preventive and therapeutic strategies for AD, and the possibility of new therapies and lifestyle interventions allows us to imagine that cognitive vitality in old age is an achievable goal. Now, we understand enough about risk factors for dementia to begin to design, test, and implement preventive strategies in clinical practice. This new knowledge makes it possible to begin to focus on the prevention of cognitive decline and the maintenance of cognitive vitality in older persons.

Achieving and maintaining cognitive vitality with (indeed, despite) aging has been a concern we have shared for some years.[2] Educating the public about the promotion and protection of cognitive health is an important goal. It requires assessment and reduction of risk factors for cognitive decline. This focus on cognitive vitality marks an expansion beyond traditional recommendations of health promotion and disease prevention, as we believe mental and physical health can be maintained and promoted. We want to emphasize that such a program is a lifelong commitment that is based on an awareness of the interactions of mind and body.

We believe this workshop report and its publication on the websites of the International Longevity Center (www.ilcusa.org) and the Institute for the Study of Aging (www.aging-institute.org) will serve the public.

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Executive Summary

More people today are living longer lives than ever before, and longevity is already commonplace in both developed and developing countries. Substantial gains in life expectancy and in the number and proportion of older people throughout the world will have a significant impact on our lives and on the programs and policies we design for the 21st century. This longevity revolution represents both an incredible opportunity and a great challenge.

Without doubt, the most prevalent and tragic affliction of old age is mental or cognitive impairment, often resulting in dementia—severe global cognitive impairment.

Cognitive aging is the term used to describe changes in memory and other cognitive functions associated with old age. Most people experience changes in memory and other cognitive functions in old age. In many cases, the cognitive changes associated with normal aging are usually mild and do not impair a person's ability to function on a daily basis. As researchers in the field of cognition, we believe that cognitive aging is potentially avoidable. Our goal is to find ways to maintain cognitive vitality in old age.

Recent studies have begun to classify the different degrees of cognitive impairment associated with aging. The earliest form of age-associated cognitive change, characterized by increased forgetfulness, is called age-associated memory impairment (AAMI). In this stage, subjective complaints of memory loss are accompanied by objective evidence of impairment. Memory loss associated with AAMI is generally slight. But it may be preventable and treatable.

A more serious form of cognitive impairment with aging is the disorder known as mild cognitive impairment (MCI). MCI is a disorder that can be identified with psychological tests that use learning and memory tasks. Individuals with AAMI do not automatically progress to MCI, but about 15% of individuals diagnosed with MCI do progress to Alzheimer's disease each year.

"Senility" is the lay term for dementia, a syndrome of cognitive impairment that affects all aspects of thinking, including abstract reasoning, judgment, language, memory, and learning. According to US studies, about 25% of people over the age of 75 and about 40% of people over the age of 80 are affected by dementia.

Alzheimer's disease is the most common cause of dementia. As individuals over the age of 85 constitute the most rapidly growing segment of our society, cognitive aging and Alzheimer's disease represent a significant and increasing social and economic burden to individuals, families, and society.

Fortunately, dementia is not an inevitable companion of old age. An alternate scenario—cognitive vitality with aging—is possible. With this in mind, the Institute for the Study of

Aging, Inc., in conjunction with the International Longevity Center—USA, Canyon Ranch Health Resort, and the National Institute on Aging, held an interdisciplinary workshop entitled "Achieving Cognitive Vitality With Aging" at the Canyon Ranch Health Resort in Tucson, Arizona on May 2 - 4, 2000. The workshop brought together expert clinicians and research scientists from diverse backgrounds and areas of expertise to address the issue of maintaining cognitive vitality with aging.

THE AIMS OF THE WORKSHOP WERE TO:

- Review current scientific and clinical knowledge of normal human cognitive aging, the biologic mechanisms that underlie this process, and risk factors associated with mental decline;
- Make recommendations for lifestyle changes to maintain cognitive vitality and prevent mental decline, based on a combination of current scientific and clinical knowledge; and
- Create a research agenda for the development of new therapies to prevent mental decline.

The absence of a complete scientific understanding of the cognitive aging process presented a genuine challenge to the group. While new findings are being published and new technology developed, there remain many secrets about aging. The group strove to identify risk factors for cognitive aging, such as those relating to nutrition, medical conditions, psychologic and psychosocial factors, lifestyle, hormones, and genetics. Participants also explored behaviors that may protect against cognitive decline, including learning new things, staying physically active, participating in leisure activities, practicing stress reduction techniques, seeking help for depression, grief, or loneliness, eating a nutritionally balanced diet, stopping smoking, reducing alcohol consumption, and seeking treatment for medical problems. The group studied data on brain plasticity (adaptivity), memory enhancers, the effects of exercise on the brain and cognition, and interventions to prevent mental decline in animal models. Potential drugs for preventing mental decline and maintaining cognitive vitality, such as acetylcholinesterase inhibitors, as well as drugs not yet approved for prevention and treatment of cognitive decline, were also discussed.

The purpose of this document is to shed light on the process of cognitive aging and to develop strategies to maintain cognitive vitality. By doing so, we hope to increase awareness of the need for more research on the subject. In addition, we hope to give physicians, policy makers, and the general public the tools to promote cognitive vitality. Our goal is to provide information that will ultimately help all individuals maintain cognitive health throughout the aging process and thereby significantly enhance their overall quality of life.

The Workshop Report

By the year 2050, there will be almost 2 billion people aged 60 years and over in the world. At that point, the population of older persons will be larger than that of children (≥14 years of age) for the first time in recorded human history.[3] This process of global aging is happening rapidly. In 1950, approximately 200 million of the world's population was 60 years of age or older. This part of the population has expanded rapidly, and the projected future expansion is dramatic (*Figure 1*).[4]

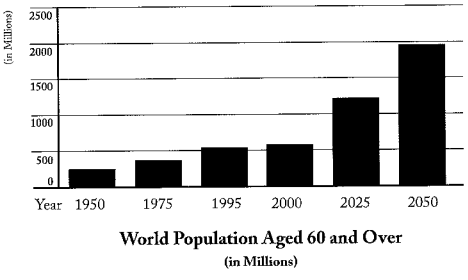

Figure 1. *Global aging: world population aged 60 and over*

What kind of future can these people look forward to? What kind of cognitive function will accompany them into their later years? Many people approach their later years worried about memory loss, shortened attention span, and incompetence in cognitively complex situations.[5] Some assume that severe cognitive decline is inevitable. In contrast, others look forward to the years past age 65 as a vital, active time in their lives. Many postpone retirement. Others choose to travel, volunteer, or begin new careers. To maintain the vitality of their bodies and minds, many follow anti-aging advice of uncertain value that they hear about on television or read about in magazines and newspapers.

People facing their later years need solid, scientific information on this complex topic—they don't need myths or false hope. The Institute for the Study of Aging, the International Longevity Center, Canyon Ranch Health Resort, and the National Institute on Aging sponsored this workshop to determine what is known and what questions remain to be answered about cognitive vitality with aging. We hope that our efforts will help people understand how cognition changes with normal aging and disease and that this understanding will enable them to make informed decisions about maintaining their own cognitive health.

WHAT IS COGNITION?

Cognition — The process of knowing. It is a combination of skills, including knowledge acquisition, attention, intuition, memory, language, perception, skilled motor behaviors, decision making, goal setting, planning, and judgment.[5]

Cognitive vitality — Good cognitive function that results from a complex combination of reserve brain capacity, acquired knowledge, and a degree of protection against brain insults. People with high cognitive vitality remain intellectually sharp as they age.[6,7]

WHY IS COGNITIVE VITALITY IMPORTANT?

Having a clear, active mind at any age is important. For older persons, cognitive vitality may make the difference between dependency and independent living. Even in less dramatic cases, cognitive vitality has a tremendous impact on quality of life.

MAINTENANCE OF COGNITIVE VITALITY HELPS INDIVIDUALS TO ...

- Enjoy everyday life fully
- Be productive (either at work, at home, or through volunteer activities)
- Acquire new knowledge
- Maintain health
- Stay involved
- Maintain independent living
- Maintain social and family relationships
- Be creative
- Face challenges
- Avoid depression

Cognitive function is tightly tied to survival. Studies have shown an association between rapid cognitive decline and increased mortality.[8] Separating "body" functions from "mind" functions is impossible, and physical health appears to be largely intertwined with mental health and function. After all, the brain is the control center for the body, and much of what we do to maintain our health is a function of "mind over matter."

THE AGING BRAIN

While we encourage an optimistic approach to cognitive vitality with aging, we cannot ignore that the brain does change with age. As it ages, the rate at which the brain can receive and process information slows. The reasons for this are not well understood. Cognition can be considered a kind of computation process in a network of billions of brain cells. During aging, some links in the network break, resulting in additional time needed to process and react to information. In most cases, a person is not even aware of this change because most common activities do not test the limits of a person's ability to process information rapidly. However, the bottleneck of slowed processing can cause other shortcomings in cognitive function,[9] such as the memory lapses that are seen in aging. In addition, complex tasks that require people to access multiple memories simultaneously may be compromised as a person ages.

DID YOU KNOW?

The activity of the brain, like the rest of the body, generally slows down with aging. This is called slowed speed of processing. Loss of function is the key factor in aging. Normally, large numbers of nerve cells are not lost.

Why does the brain "slow down"? One suggestion is that several processes such as those listed below can result in reduced cognitive vitality.

- ***Inflammation*** — In the brain, inflammatory responses are part of the natural repair process following an injury or infection. However, chronic, uncontrolled inflammation may tip the balance toward brain injury rather than brain repair.[10]

- ***Oxidative stress*** — Metabolic processes produce oxidants (chemicals that damage cells, molecules, and cellular components such as membranes and mitochondria) and antioxidants (chemicals that protect tissues from oxidants). When long-term oxidant activity outweighs long-term antioxidant activity, brain damage occurs.[11]

> ***Antioxidants*** — Chemicals such as vitamins C and E that may protect neurons (nerve cells) by decreasing the adverse effects of reactive oxidants and may promote cognitive vitality.

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- ***Hormonal Changes*** — Estrogen acts as a neurotrophin, which means that it protects neurons from damage and promotes the production of new neurons in the brain.[12] Animal studies show that the postmenopausal estrogen decline in women may be one of the factors that accelerate the occurrence of age-related cognitive impairment.[13]

> ***Neurons*** — Nerve cells, which communicate information in the body. The brain has billions of neurons, which give it a sizable reserve capacity to compensate for neurons that are damaged or destroyed.[14]
>
> ***Neurogenesis*** — The production of new nerve cells. Recent work indicates that new brain cells can be made even in advanced age.

- ***Amyloid deposition*** — Beta-amyloid (Aß) is the primary protein that comprises the senile plaques that form in the brains of Alzheimer's disease patients. Deposits of this protein in the brain cause brain injury.[11]

> ***Senile plaques*** — Deposits of beta-amyloid in the brain that cause brain damage associated with the progressive cognitive decline characteristic of Alzheimer's disease.
>
> ***Alzheimer's disease*** — A disease characterized by progressive cognitive decline caused by brain changes such as the degeneration of neurons and the formation of senile plaques and neurofibrillary tangles (abnormal debris inside brain cells).

Is Cognitive Decline Something Everyone Should Expect?

Just as the physical effects of inflammation, oxidative stress, hormonal changes, and amyloid deposition vary from person to person, cognitive functioning varies among people and over time. Mental function generally follows a continuum (*Figure 2*). Some people maintain cognitive vitality as they age, showing only small losses in mental function. While some degree of memory loss can be expected, cognitive or mental decline in some individuals becomes abnormal, beginning a progression that may ultimately end with dementia.[15] The initial stage of this decline may be age-associated memory impairment (AAMI). In this stage, people have subjective complaints and objective evidence of memory loss. Diagnosis of AAMI is difficult. The next stage in the continuum is mild cognitive impairment (MCI), which is marked by even greater memory loss. Specific psychological testing can determine whether the memory loss falls within the normal range or can be

diagnosed as MCI. MCI may progress to dementia. While AAMI and MCI are characterized by memory loss alone, dementia refers to mental decline severe enough to keep a person from functioning normally. It is characterized by memory loss and other cognitive dysfunction (such as impaired abstract thinking). Many people fear dementia. It robs them of their personalities, their ability to interact with others, and their ability to function independently. Alzheimer's disease is the most prevalent cause of dementia in older people.[16]

high cognitive function. One study showed that high-functioning older adults smoke less, exercise more, and are more likely to engage in volunteer activities than lower-functioning older adults.[21] These associations between certain cognitive behaviors and high cognitive functioning are not unexpected. As we shall discuss, people can take behavioral steps to prevent or postpone mental decline.

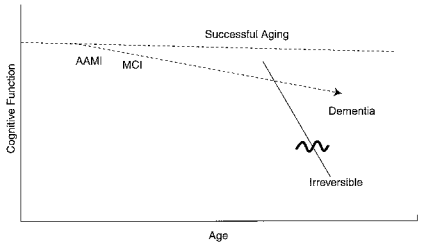

Figure 2. *Model for phases of brain aging*

In this model, some degree of cognitive impairment is associated with "successful aging." Against this background, abnormal changes can occur that progress through age-associated memory impairment (AAMI) and mild cognitive impairment (MCI) to dementia. At some stage in dementia, irreversible damage apparently occurs. Adapted from Cotman 2000,[10] with permission.

Dementia is not a normal part of aging, as it only affects about 3% to 10% of people over age 65.[17,19] Also important to note is that not all people diagnosed with MCI will end up with dementia and that long periods may pass before this condition deteriorates into dementia.[20] While most people over the age of 70 experience some degree of cognitive decline, particularly short-term memory loss, many people age without any abnormal cognitive decline. Many centenarians (men more than women) maintain

Dementia — A condition marked by progressive cognitive impairment. This condition, by definition, is severe enough to disrupt daily living.[17]

Mild cognitive impairment — Perhaps a transitional stage between age-associated memory impairment and dementia, characterized by noticeable memory loss but without other changes in cognitive abilities. Not all people with mild cognitive impairment develop dementia.[18]

Who Is At Risk For Cognitive Decline?

Certain factors make some of us more likely than others to experience cognitive decline. People need to be aware that some factors cause potentially reversible mental decline and should be addressed by a physician. These include adverse drug reactions, overmedication, depression, metabolic and endocrine (hormonal) disturbance, tumors, trauma, alcoholism, eye and ear problems, and infection.[23-24] Other risk factors for dementia, which is not a reversible condition, may be genetic or environmental.[25] These factors should be considered in long-term prevention strategies.

Risk factors vary—some can be changed or modified, and some cannot. The following table lists some risks for cognitive decline and/or dementia and categorizes them.

GENETIC FACTORS

Female gender [26]
ApoE4 genotype [27]

MEDICAL COMORBIDITIES

Hypertension [28]
Heart disease [28]
Diabetes [29]
Elevated low-density lipoprotein cholesterol [30]
High homocysteine levels [31]
Transitory ischemic attacks (TIAs) [28]
Head trauma [32]
Environmental exposure to toxins (particularly lead) [33]

LIFESTYLE CHOICES

Smoking [26,28]
Substance abuse, including alcohol and illicit drugs [34-39]

PSYCHOLOGICAL/PSYCHOSOCIAL FACTORS

Low educational achievement [26,40-43]
Lack of physical activity [40]
Lack of social interaction/leisure activities [44]
Excessive response to stress (excessive cortisol levels) [45]

Factors/Interventions That Promote Cognitive Function

Researchers are exploring ways to postpone and/or treat mild dementia. If successful, these therapies may have a broader use and help to keep the mind functioning well as people age. Also, people may be able to reduce the risk of cognitive decline and achieve cognitive vitality by adopting certain preventive strategies that are discussed below.[2]

Lifelong Learning and Training

Animal studies have shown that intellectual stimulation actually promotes brain growth.[46] Studies in people have demonstrated that lower education levels or low language ability in early life are associated with cognitive impairment and dementia in later years.[41,47] Education has been found to protect against cognitive decline even in those younger than age 65.[48] Indeed, adult education and educational/intellectual stimulation later in life may help to maintain cognitive health.

Fortunately, the brain maintains its plasticity (adaptivity) even into very old age. In the very old, repeated training can be effective in sustaining higher levels of cognitive performance.[49] Simply re-testing older subjects during training exercises enhances memory performance.[50] Training may be formalized or it may consist of doing memory exercises, such as crossword puzzles.

Brain plasticity — The ability of the brain to change in response to stimuli (e.g., learning). Despite myths to the contrary, the brain can rewire itself, even into old age, and some areas of the brain may be able to add new cells in response to stimulation.

Exercise

Lack of physical activity has emerged as a risk factor for cognitive decline. Encouraging people to continue engaging in enjoyable physical activities as they age is another way of promoting cognitive vitality. Several studies have shown that exercise has a beneficial effect on the brains of older persons. Active older adults demonstrate improved blood supply to the brain, higher cognitive test scores in some areas, and improved reaction time. Even older adults with physical and emotional impairment benefit from exercise training. As the American workforce ages, employers may find it beneficial to encourage activity and provide exercise opportunities during the workday, as this will help to improve productivity, health, and cognitive function.[40,51-54]

Did you know?

Moderate aerobic activity, like walking, improves function in executive tasks, such as problem solving, in older people who previously had not exercised.[55]

Daily Activities

A rich and stimulating work environment may help maintain cognitive function. This should be an important consideration for a person thinking about retirement.[56] Social and nonwork activities are also correlated with the risk of cognitive decline in older adults. For this reason, older people should be encouraged to keep working and/or to participate in activities like traveling, knitting, gardening, or volunteering. They should also be encouraged to participate in group activities that provide opportunities for social interaction.[44]

Stress Reduction

Stress reduction techniques have also proved to be important as part of the daily activities of older individuals. Animal studies have shown that chronic stress alters brain structure and can reduce the body's ability to maintain normal physiologic function, which may, in turn, affect cognitive function.[57,58]

Sleep

Older people are often plagued with sleep problems that can negatively affect cognitive function. Controlling sleep disturbances and increasing REM (rapid eye movement or dream) sleep are associated with preserved cognition and function.[59,60]

Emotional Stability

Studies suggest a connection between cognitive and emotional health. High-functioning older adults report fewer emotional problems and score higher on scales of self-efficacy. Older people who have been married show greater emotional stability and higher cognitive function than their peers who never married.[61] The stress of depression in older adults may actually result in injury to the brain and may be associated with the increase in the rate of suicide among this population, particularly among white men.[62] Health care professionals and patients, therefore, need to be alert to the symptoms and effects of depression and make sure it is properly treated.[21,63]

Nutrition

Nutritional intervention has been investigated as a way to delay and/or prevent cognitive impairment. Some animal studies suggest that reduced caloric intake may protect against the effects of aging. In one study of mice, data showed that a nutritious but restricted calorie diet, introduced at weaning, did not reduce adult brain weight but did reduce adult body size. This study also demonstrated in animals that caloric restriction at midlife does prolong cognitive function, although other data do not support this finding.[64] At present, doctors do not generally promote dieting in older individuals because it may increase frailty or mask disease-related

weight loss. A balanced diet is vital to preserve general health and vitality.

Researchers are also looking at the role of antioxidants in preserving cognitive vitality and preventing dementia. Antioxidants act as scavengers, protecting the body against free radicals that can damage brain cells.[65] Free radicals are highly reactive substances that cause damage through chemical processes such as oxidation. Vitamins C and E, along with beta carotene, act as antioxidants. Among people aged 65[65] and older, those with a higher intake of these antioxidants have better memory performance, suggesting that antioxidants may help prevent progressive cognitive impairment.[66] Currently, research is under way to investigate whether vitamin E can help prevent or delay Alzheimer's disease in older people with MCI.[67]

Though more research is needed in this area, eating antioxidant-rich fruits and vegetables and/or taking a daily multivitamin may be beneficial. But like all chemical substances, nutrients and other food components can have negative effects if taken in excess. For example, the upper limit of intake for vitamin C for adults over age 50 is 2000 milligrams (mg) a day; more than this can cause renal dysfunction and diarrhea and distort the results of some laboratory tests. The upper limit recommended for vitamin E is 1000 mg a day.[68]

The Institute of Medicine's Food and Nutrition Board recently released the newest dietary reference intake values, which gives suggested daily doses and tolerable upper limits for vitamins C and E. The report does not recommend a daily or upper intake level for carotenoids such as beta carotene, so people should be careful not to take them in high doses. The report recommends taking beta carotene supplements only for the prevention and control of vitamin A deficiency.[68]

The Effect of Medical Problems/ Interventions on Cognition

As people age they often need to cope with medical conditions that may affect cognition. The effects of some conditions, like stroke, may be obvious, while other changes, like hormone levels that are reduced in aging, may affect cognition in more subtle ways.

Injuries

Brain injuries occur most frequently in two age groups: people aged 15 to 24 years and people aged 75 and older. Brain injury can result in lifelong impairment of physical, cognitive, and psychosocial functioning. Many brain injuries are not treatable, so prevention through precautionary measures such as wearing seat belts, bike helmets, and reflective clothing should be the main focus.[69] In addition, research has shown that professional soccer players who frequently "head" the ball often suffer from brain injury. With the growing number of children participating in youth soccer programs, parents, children, and coaches should be educated about the potential negative effects of this technique, and it should be discouraged by parents and coaches alike.[70] Boxing is another sporting activity associated with a risk of brain injury and dementia. In general, people who participate in athletic activities should take caution to ensure that the head is protected.

Alcohol and Smoking

Some studies have suggested that nicotine may improve information processing and memory.[71] Current research is investigating new drugs that mimic the effect of nicotine on cognitive function.[72] However, cigarette smoking has numerous long-term adverse effects on the heart, lungs, and brain, and a number of studies show negative effects of smoking on cognition.[73]

Excessive alcohol consumption can cause nerve cell death, which may contribute to dementia

and is associated with rapid cognitive decline in Alzheimer's disease patients.[74] Research on people who have Alzheimer's disease, however, excludes people with known heavy alcohol use, leaving many questions about the association of alcohol and Alzheimer's disease unanswered.[75] Moderate alcohol consumption may help prevent cognitive decline, possibly through effects on the cerebral blood vessels.[76] But the evidence is not conclusive, and recommending that older individuals use alcohol for medicinal purposes is risky, since alcoholism is a significant problem in this age group.[77]

Hormonal and Drug Supplements

Alzheimer's disease is more common in women than in men, and researchers have found a relationship between estrogen deficiency and Alzheimer's disease. Estrogen may play a role in maintaining neuronal health and some aspects of cognitive function in older women.[78] Findings suggest that estrogen replacement therapy enhances new learning and helps maintain verbal memory. Results from animal and human studies of estrogen replacement therapy are promising, but the findings are not conclusive.[12,17,79] Further research is needed to determine whether estrogen replacement therapy can protect women from cognitive decline. Those considering hormone supplements may wish to consider the potential benefit for preventing cognitive decline when assessing the risks and benefits of these therapies. Studies are also ongoing to evaluate the effect of testosterone on cognitive function with aging.

Dehydroepiandrosterone (DHEA), a natural precursor of estrogen and testosterone, has been advertised as a supplement to boost memory and as a cure for many ills of aging. Though DHEA levels do decline as people age, research does not support these health claims.[80] Until further research is carried out, DHEA is not recommended for the prevention of cognitive decline or for enhancement of cognitive function in older people.

Melatonin, a hormone produced by the pineal gland in the brain, is a highly advertised over-the-counter substance purported to improve the quality of sleep. Some studies show that melatonin levels fall with age, but others do not. Some scientists think that lower melatonin levels may be associated with sleep disorders in some older people, which may in turn cause cognitive impairment. However, until well-controlled clinical trials are conducted, melatonin is not recommended as a long-term supplement.[19]

Human growth hormone levels also decline as we age.[81] Half of all people age 70 and older have some deficiency of this hormone. Studies investigating whether human growth hormone can improve cognitive functioning have had mixed results. More studies are needed before treatment with this hormone can be recommended for maintaining cognitive vitality,[19] especially since the long-term adverse effects of this treatment are unknown.

Hypertension, Diabetes, and Vascular Disease

Multiple chronic diseases have been associated with memory impairment. Hypertension (high blood pressure) and heart disease affect almost one third of today's older population.[19] Hypertension and other forms of vascular disease may contribute heavily to vascular (multi-infarct) dementia, the second most common form of age-related dementia, which accounts for approximately 15% of all late-life dementias.[23] Blood pressure control is important to a person's overall health, and effective treatment of hypertension is likely to prevent cognitive decline by reducing the risk of stroke.[82] More research is needed to definitively determine whether treatment of hypertension prevents cognitive decline. Conditions associated with heart disease, such as atrial fibrillation, myocardial infarction, and congestive heart failure, have been linked to cognitive decline.[83,84]

Vascular dementia — A condition caused by multiple mini-strokes that result in brain damage and loss of cognitive function. It is the second most common type of dementia. Risk factors for this condition include myocardial infarction (heart attack), hypertension (high blood pressure), atherosclerosis, diabetes mellitus, obesity, a sedentary lifestyle, and smoking.

Daily low-dose aspirin therapy is often recommended for people at risk for heart attack and stroke. Some research has shown that aspirin is moderately beneficial in preventing cognitive decline.[85] Other studies do not show a difference between aspirin users and nonusers.[86] Atherosclerosis is also a risk factor for dementia and has been shown to be associated with poor cognitive function.[87] Therefore, eating a low-fat diet and, if necessary, taking cholesterol-lowering medication to control this condition may protect against cognitive decline. More research is needed to assess whether treatment of atherosclerosis will improve cognitive functioning.

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Diabetes, a common condition in older people, is a significant cause of sickness and death. Older people with diabetes may have impaired cognitive function.[29] However, the issue of the relationship between cognition and elevated glucose (blood sugar) levels in diabetes is difficult to interpret, since the brain needs glucose for cognition.[88] Glucose, which is the body's main source of energy and is produced from digested food, such as starch, cane sugar, maltose, and lactose, has been shown to be effective in enhancing cognitive performance in healthy young and older adults as well as in individuals with Alzheimer's disease.[89] Research suggests that cognition may be impaired in hypoglycemia (low blood sugar) and in hyperglycemia (high blood sugar), both complications of diabetes.[90] Indeed, poor metabolic control (sustained hyperglycemia) in people with diabetes has been linked to reduced cognitive functioning.[91] Given this relationship, studies of new drugs for treating diabetes should include cognitive function as an endpoint, especially if these drugs are likely to cause hypoglycemia. Furthermore, diabetes and poor control of blood glucose levels have been shown to contribute to cardiovascular disease and stroke, which are also risk factors for impaired cognitive functioning.[92] People with diabetes should avoid both hyperglycemia and hypoglycemia in order to preserve cognitive function.

Summary of Recommended Approaches to Maintaining Cognitive Vitality

The varied approaches to achieving and maintaining cognitive vitality that have been discussed are summarized in practical terms in the following table.

Behaviors that May Protect Against Cognitive Decline

- Keep challenging yourself to learn new things ("Use it or lose it")
- Stay physically active ("Move it or lose it" may be truer than we realize!)
- Remain socially active
- Participate in leisure activities. Practice daily stress-reduction techniques, such as meditation and/or yoga. Get a restful night's sleep when possible
- Seek out the help you need if you suffer from depression, grief, or loneliness
- Eat well, but not too much; keep calorie intake moderate. Eat antioxidant-rich fruits and vegetables
- Take a daily multivitamin/mineral supplement but avoid taking excessive amounts
- Be safe and avoid head trauma—fasten seat belts, use a bike helmet and other safety gear, and avoid "heading". Boxing is strongly associated with a risk of brain injury and dementia
- If you smoke, stop!
- If you drink, use alcohol in moderation—less is probably better. Do not take dehydroepiandrosterone (DHEA), human growth hormone, melatonin, or other over-the-counter anti-aging supplements without consulting your physician
- Make sure you receive proper treatment if you have high blood pressure, high cholesterol, or other cardiovascular conditions
- Make sure to keep diabetes, heart disease, and other medical conditions under control
- Use sensory aids (hearing aids, reading glasses, etc.) to maximize interaction with the environment
- If you are a woman, consider estrogen replacement therapy carefully and discuss it with your doctor

Pathologic Changes Leading to Cognitive Dysfunction and Possible Therapeutic Interventions

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Pathologic Change	Therapeutic Intervention
	Cognitive Enhancers
Reduced neurotransmitter production/function (fewer or weaker signals between nerves)	Acetylcholinesterase inhibitors[*][93-98]
	Nicotinic agonists[89]
	Glutamate modulators[93,100-102]
	Muscarinic (M1) agonists[103]
	Muscarinic (M2) antagonists[103]
	Huperzine A[104]
	Gingko biloba[105]
	CREB[†] enhancers[106-108]
	Disease Modifying Agents
Formation of senile plaques	Amyloid vaccine[109]
	Inhibitors of synthesis and production of beta-amyloid precursor[110]
	Beta and gamma secretase inhibitors[110]
	Alpha secretase enhancers
	Inhibitors of amyloid fibrillogenesis and aggregration
Neural dysfunction/cell death	Glutamate antagonists
	Neurotrophins (NGF, BDNF, AIT-082)[111-114]
	Caspase inhibitors
	Glucocorticoid antagonists
Decreased hormonal function	Estrogen replacement[17,115-122]
	Testosterone replacement[123,124]
	Other hormones: DHEA[‡], melatonin[79,81,125,126]
Inflammation	Anti-inflammatory agents (e.g., NSAIDs[§])[127,128]
Oxidative stress/free radical production	Antioxidants (e.g., vitamin E, vitamin C)[129,130]
Elevated homocysteine levels	Nutritional supplements (vitamin B6, vitamin B12, and folate)

[*]These are the only types of drugs approved by the Food and Drug Administration for treatment of Alzheimer's disease. [†]Cyclic response-element binding protein. [‡]Dehydroepiandrosterone. [§]Nonsteroidal anti-inflammatory drugs.

The Future of Drug Therapy to Maintain Cognitive Vitality

Three medications (all acetylcholinesterase inhibitors) are available and several are currently under development for the treatment of cognitive disorders and Alzheimer's disease. These medications fall into several categories based on which part of the Alzheimer's disease process they target.

Most of these types of medications are being examined for treatment of dementia, but some are under study for earlier stages of cognitive decline, particularly the MCI stage.[120] But what about drugs to improve cognition in people who do not have MCI or Alzheimer's disease but are primarily suffering from "normal cognitive aging"? Disease-modifying agents may be useful to prevent Alzheimer's disease and cognitive decline with aging, but much research needs to be done.

Some interest is growing in this area of cognitive enhancement.[5] An example of a cognitive enhancer is cyclic AMP response-element binding protein (CREB). With cognitive training this protein is produced in the brain. Its expression has been linked to long-term memory formation in animals.[106] Eventually, scientists may be able to develop methods of enhancing brain levels of proteins, such as CREB, that might reduce the amount of time and effort needed to commit things to long-term memory. However, the ethics of using cognitive enhancers, such as Ritalin®, in the general population is an issue of debate because their long-term effects are unknown. Double-blind, placebo-controlled trials to test the effects of drugs on cognitive decline and dementia are necessary before drugs can be prescribed to treat these conditions.

Future Directions for Cognitive Health

Our rapidly aging population requires us, as a society, to make fundamental changes in policy and research to ensure that older adults maintain the level of cognitive vitality needed to lead productive, satisfying lives.

Health care practitioners can contribute to the promotion of cognitive vitality in the following ways:

- Make cognitive vitality an important goal. Practitioners should talk with patients about how different conditions or treatments affect their minds. Some patients may become motivated to change their behavior (such as smoking) or to take medications to improve other conditions (such as diabetes or hypertension), if they think those interventions will keep their cognitive faculties intact.
- Do not assume that the cognitively impaired patient cannot be treated. All individuals reporting cognitive changes with aging should be evaluated. Practitioners should look first for causes of potentially reversible impairment and treat them. If there are none, patients should be referred for a diagnostic exam. Relatives of dementia patients should be directed to the Alzheimer's Disease Education and Referral Center (ADEAR) and the Alzheimer's Association for information and support services.
- Make sure patients do not have unrecognized or untreated sensory impairments that contribute to their problems. Practitioners should also use technologies that help those with sensory impairment to interact with their environment (e.g., hearing aids).[131]

Society at large can promote educational endeavors and implement policy changes to help its members achieve and maintain cognitive vitality. Some of these changes can be instituted by community organizations; others require the government to change its policies and promote

new types of funding. Specific interventions include the following:

- Local communities should institute "get-up-off-your-apathy" agendas to encourage people to get moving intellectually, physically, and socially as a means of promoting cognitive vitality.
- The government should support the development of a national population database that studies people longitudinally (over time) to assess cognitive function.[1] Diagnosis of patients for inclusion in such a study should be covered under diagnostic-related group (DRG) codes. A concerted effort should be made to include cognitive outcome measures in health-related longitudinal studies (e.g., longitudinal cardiovascular studies).
- The NIA should continue to develop interdisciplinary consortia to encourage researchers with different areas of expertise to come together to address the research issues related to achieving and maintaining cognitive vitality,[1,132] in addition to, but separate from, the considerable amount of funding currently directed to Alzheimer's disease. Such concerted research efforts should continue to be used for studies such as the NIA Baltimore Longitudinal Study of Aging.

Researchers also need to target specific objectives to advance knowledge about cognitive vitality. The following will facilitate the study of certain issues:

- Better description of the specific physical changes that occur in the brain with normal aging and those that occur in older people with MCI. These changes should be examined on the molecular, cellular, organ system, and individual level.
- Genetic studies. The role of genetic factors requires further study.
- Sensitive biologic markers of normal cognitive decline.[1] Measures of patient behavior are often not sensitive enough to track changes over time, particularly with cognitive therapies. Biologic markers that can be used in this way need to be developed.
- Additional postmortem studies. Psychological tests conducted over the course of normal aging should be paired with autopsy results so that the functional changes can be linked to anatomic changes.[132]
- Animal studies. Better animal models of normal cognitive aging need to be developed. A rapid test for cognitive impairment in the rat should be developed. Aging models and testing should be standardized across laboratories doing cognition research. Improved imaging systems are needed so that small animal brains can be examined.
- Examination of the effects that social and cultural conditions (i.e., education, early life experiences, sense of control or worth, etc.) have on cognitive vitality later in life.
- Double-blind, placebo-controlled clinical trials to assess the effects of putative agents on cognitive decline and dementia.

Conclusions

Cognitive vitality is critical to optimal aging. Although many questions about the aging brain remain, we now have suggestions for preventive strategies and interventions that promote cognitive vitality. With these in mind, people can take concrete steps to maintain their intellectual vigor. Physicians and other health care providers can play a major role in assisting individuals to achieve and maintain cognitive vitality. As our knowledge base increases, the options for promoting cognitive health are also likely to expand to meet the demands of a growing number of people who will want to remain cognitively vital in their later years.

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WORKSHOP
REPORT

Maintaining HEALTHY Lifestyles: A Lifetime of Choices

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The International Longevity Center – USA
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PREFACE

Maintaining Healthy Lifestyles

By Robert N. Butler, M.D.
President and CEO
International Longevity Center

Why did the International Longevity Center and Canyon Ranch decide to hold this workshop which assembled some of America's finest social and behavioral scientists and leaders in medicine and public health to consider what we presently know about maintaining healthy lifestyles? *Healthy People 2000* expressed the Surgeon General's aspirations for the well-being and health of the American people and laid out some 300 health targets. However, only 15% have been met.

This cannot to be explained totally by a lack of desire on the behalf of the American people. People initiate appropriate and new health habits daily. The problem is maintaining them. What are the obstacles? What have we learned about methods to assist people in their desire to enjoy a healthy lifestyle and well-being?

Why did this workshop focus on older adults? Most of what was discussed and recommended applies to persons throughout the entire life course. But it is important to emphasize that it is never too late to introduce healthy behavior and it is always too early to stop. Furthermore, it is actually easier to measure behavioral change and outcomes in the older age group. When you study interventions introduced early in life you have to wait many years to determine outcomes.

We worked toward consensus in all age groups. For example, the Baby Boomers, now 35 to 54 years of age, are a generation at risk. Moreover, today's children receive minimal opportunities for physical education at school and have been involved in the sedentary lifestyle of television viewing and cyberspace.

Why did we focus upon physical activity, diet and smoking? These are the "big three", the most powerful in their effects upon and in the causation of disease. Moreover, they are within our power to do something about them.

What have we learned? That there are many simple, practical strategies within our reach. Our big task is to move beyond communities of affluent Americans, who are generally better educated in health promotion and disease prevention. We hope that our recommendations for a national effort might be realized.

We respect the efforts of U.S. Surgeon Generals and understand the importance of identifying the many health targets that must ideally be met. However, we believe that by focusing on these three activities alone in a major national effort involving the public and private sectors, we may do better than we have done through more diffuse efforts to address hundreds of targets. This becomes all the more meaningful when we look at the new *Healthy People 2010* report that details over 700 targets.

The maintenance of healthy lifestyles is not just a personal matter. It is also a matter of national importance. Health costs continually rise and the quality of life of the American people is at issue.

In the last century we gained more years than had been attained during the preceding 5000 years of human history. It is likely that there will be further additions to longevity in this century. The longevity revolution appears to be a continuing process. It is all the more important that, living longer, we should live better.

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Executive Summary

Toward A Healthier Society: The Current Status

Americans can applaud many favorable health trends over the past century. In most communities infant and maternal deaths are rare, life expectancy is at an unprecedented high, significant declines in expected disability among older persons have been noted, and the number of centenarians is growing dramatically. Yet, we are missing critical opportunities for enhancing the quality of these added years of life.

The links between health and lifestyle behavior are now indisputable. Heath risks such as smoking, physical inactivity, being overweight or obese, consumption of high fat diets, and inadequate fruit and vegetable intake are major determinants of morbidity and mortality. Contrary to popular assumptions that old age diminishes the importance of such behaviors, there is no outliving the effect of these risks. Lifestyle behaviors remain potent predictors of health and function throughout the life-course and have negative health consequences even for older adults.

There are two primary challenges: 1) how to sustain the adoption of healthy lifestyles over time, and 2) how to reach all Americans, especially those with the greatest health needs. The problems are complex — and the solutions must be comprehensive — drawing upon individuals, families, health care professionals, communities, and society as a whole.

Expert Panel Convened

In December of 1999, a group of experts in medicine, behavioral and social sciences, and public health met at the Canyon Ranch Health Resort in Tucson, Arizona to: 1) review the state of the art of what is known about initiating and maintaining recommended healthy behaviors and lifestyles; 2) discuss implications of research for designing the best individual, community and societal behavioral change programs; 3) identify gaps in knowledge and recommend the next research and practice steps; and 4) recommend strategies for translating research outcomes into practice and policy.

This report highlights the panel's discussions concerning the following major issues:

- Social and environmental influences on healthy behaviors and lifestyles.
- Current knowledge about the design and implementation of successful behavioral change interventions.
- Models of successful behavioral change programs.
- The complexities of maintaining health behavior change over a lifetime.
- Gaps in research knowledge and future research recommendations.
- The next generation of behavioral change interventions.
- The translation of current research findings into practice and policy.
- The formulation of concrete actions.

Conceptualizing a Contextual Approach

Characteristics of "everyday life", such as the number and types of social contacts and the characteristics of the immediate physical environment, affect a person's levels of health, functioning and health behavior. A public health or ecological approach represents a promising strategy to improve the health and well being of populations or communities of older people.

Successful Intervention Strategies

What we know about interventions to effect changes in behavior: A synthesis of the scientific literature

Interventions that have been developed and evaluated in the health promotion field typically have been aimed at a specific level of impact—for example, the personal or interpersonal level, the organizational or institutional level, the health care level, the environmental level, and the policy or legislative level.

- Successful intervention strategies aimed at individuals or small groups typically have included the use of self-regulatory skill training with ongoing social support and guidance from a trained interventionist. Self-regulatory skill training includes realistic goal setting, self-monitoring of target health behaviors, use of feedback and social support related to the behavior of interest, relapse prevention or preparation training.
- There is a growing body of evidence showing that worksite interventions involving combinations of competition, individual and group goal setting, and the support of management can help to change health behaviors, particularly for behaviors involving physical activity.
- Primary care physicians are learning how to deliver more effective messages to help their patients quit smoking, increase their physical activity, or change their dietary practices. Nurse care management interventions have also been successful using proactive behavioral management strategies such as collaborative, patient-centered goal setting and follow-up support for chronic disease management (especially for heart disease, asthma, and diabetes.)
- Successful interventions involving point-of-choice information have had a positive effect in health behavior areas of smoking, nutrition, and physical activity. For example, successful point-of-purchase interventions which encourage people to order health-promoting foods have been conducted in restaurants, cafeterias, and related venues.
- Policy/legislative level of impact strategies whose aim it is to deter cigarette smoking have generally met with resounding success. Such policies include smoke-free building and transportation regulations, and statewide cigarette tax increases. Fewer regulatory policies have been put into place or evaluated in the dietary and physical activity arenas.

Principles of Health Behavior and Behavior Change

- Initiating and maintaining healthy behaviors is best accomplished by taking advantage of the multiple opportunities for change in one's environment.
- The maintenance of healthy behaviors requires planned follow-up.
- The goals of healthy behavior change should reflect a partnership between the participant and the provider and be stated in concrete terms.

- The goals of behavior change should be conceptualized as moving targets that are influenced by personal/interpersonal factors, life situations, the environment, and policy.
- Interventionists should consider why people change, and in this context evaluate the ability of their interventions to effect change.

Models of Successful Change

This report presents three case studies to demonstrate how behavioral change interventions can increase the adoption of healthier lifestyles, resulting in improved health outcomes and lower health care costs. These case studies (smoking cessation; self-management of dietary behaviors; and exercise enhancement in frail older adults) help to illustrate what successful interventions look like; the kinds of strategies that have been employed; the populations targeted; and the kinds of outcomes achieved.

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Complexities of Maintaining Health Behavior Change Over a Lifetime:

Variability in Health Behaviors, Interventions and Populations

Significant progress has been made with the development of detailed, personally tailored behavioral interventions for several health promotion and disease prevention goals (e.g., physical activity, dietary change, cancer screening, smoking cessation.) Computer-assisted interventions allow interventionists to customize their messages. These have been delivered via a variety of modalities, including individually tailored letters and newsletters, interactive touch-screen computer kiosks in medical care and other settings, the Internet, automated voice messaging, and other communication channels.

While these advances are impressive, much still needs to be learned about types of tailoring, the factors which are important for different persons, and the cost-effectiveness of different tailoring methods and interventions.

How Can We Motivate Long-term Adherence and Interconnections Across Behavioral Domains?

In all of our efforts to encourage older or middle-age adults to engage in regular and meaningful lifestyle modifications, it is clear that we are more successful in gaining initial levels of interest and participation than we are in sustaining interest and participation over the longer term. Far more research has been devoted to the study of "early successes" than to "long-term maintenance" of behaviors and lifestyle changes. Not only has there been more research on early success in attaining measurable change in health behaviors, but most programs or interventions with these goals are able to register these early successes among their participants, and most report high levels of satisfaction as well.

Research Gaps and Future Research Directions

Additional research is needed on:

- Tailoring by risk, behavior and developmental stage
- Targeting multiple behaviors
- Promoting clinical and health system interventions
- Enhancing the social and physical environment

Testing Innovative Approaches to Behavioral Change Interventions and Maximizing Their Adoption

This report identifies several promising interventions that are now ready for further

testing or translation to broader audiences. Spreading the benefits of such programs to wider communities of potential participants is the next challenge and a priority for national prevention policy.

Program evaluation should include an assessment of participation rate and the representational range of participants; its effectiveness under non-research conditions; the percent and representational range of settings willing to attempt an innovation; implementation or intervention integrity under field conditions; and finally, maintenance of both individual behavior change and organizational-level delivery of services. A broad range of outcomes should be considered--behavioral outcomes, health and functional outcomes, quality-of-life outcomes, and health care use and cost outcomes.

The ultimate outcome of interest is clinically meaningful results that produce differences in everyday life functioning.

Action Steps

The expert panel identified many of the factors that directly link the health of Americans to lifestyle patterns. Lifestyle choices are shaped by factors found within legislative, social, economic and physical environments — many of which are changeable as evidenced in the research literature.

The urgent challenge that lies before us is the mobilization of public and private sector resources to improve the population health of this country through evidence-based programmatic strategies that will reach large segments of society. Recommended actions include:

- National Healthy Lifestyle Campaigns
- Network Centers for Healthy Lifestyles
- International Center for the Initiation and Maintenance of Healthy Lifestyles
- International Conference on the Initiation and Maintenance of Healthy Lifestyles
- Strengthening the national research infrastructure on healthy lifestyle and longevity
- Changing mainstream health care practices related to lifestyle change motivation and disease prevention

Practical Strategies for a Healthier Lifestyle Through Autonomy and Self Management

- Establish a goal and make a contract with yourself. The three vital areas to target are nutrition, tobacco cessation and physical exercise.
- Personalize your program to address special needs or health risks, such as diabetes, high blood pressure, high cholesterol.
- Find convenient and inexpensive ways to achieve your goals.
- Self-monitor your efforts. If your goal is weight loss, write down exactly what you eat. If your goal is to become more physically fit, wear an electronic-based pedometer to clock the number of steps you take in a given day, whether you walk, jog or run.
- Build healthy habits and activities around your schedule. Establish routines that are environment-friendly, at the workplace, school and home.
- Find a role model to emulate in adopting a healthier lifestyle.
- Establish a peer-support system. Mutual support encourages compliance, whether it be a partner, a club or family members.
- Establish a professional-support system with a physician or fitness trainer who can offer guidance and support.
- A positive cost-benefit ratio is critical to behavior change.
- The adoption and maintenance of healthy behaviors requires basic skills that can be taught.

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The links between health and lifestyle behavior are now indisputable. Heath risks such as smoking, physical inactivity, being overweight or obese, consumption of high fat diets, and inadequate fruit and vegetable intake are major determinants of morbidity and mortality.

Contrary to popular assumptions that old age diminishes the importance of poor health habits, there is no outliving the effect of these risks. Lifestyle behaviors remain potent predictors of health and function throughout life. Health-impairing behaviors have negative health consequences even for people who live well past their sixties. The good news that "It is never too late to adopt a healthy lifestyle" must be tempered with the reality that behaviors need to be sustained over a lifetime for maximal benefit. The bad news is that "It is always too soon to quit!" as health benefits rapidly fade when healthy behaviors are terminated.

In recent years greater attention has been placed on understanding the determinants, natural history and consequences of health-promoting and health-impairing behaviors. This is important for designing and implementing effective strategies for encouraging Americans to initiate and sustain recommended healthy practices. Our public health messages are reaching many people.

However, there are two primary challenges: 1) how to sustain the adoption of healthy lifestyles over time, and 2) how to reach all Americans, especially those with the greatest health needs. The problems are complex and the solution must be comprehensive. They must draw upon individuals, families, health care professionals, communities, and society as a whole.

EXPERT PANEL CONVENED

In December of 1999, a group of experts in medicine, behavioral and social sciences, and public health met at the Canyon Ranch Health Resort in Tucson, Arizona to: 1) review the state-of-the-art regarding what is known about initiating and maintaining recommended healthy behaviors and lifestyles; 2) discuss

implications of research for designing the best individual, community and societal behavioral change programs; 3) identify gaps in knowledge and recommend the next research and practice steps; and 4) recommend strategies for translating research outcomes into practice and policy.

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The Current Health Risk Report Card: Promise and Challenges

Physical Activity/Exercise

The Good News: Programs are recognizing the health benefits of a wide range of physical activities that take into account individualized needs and interests. For example, emphasis has shifted away from intensive aerobic exercise for everybody. Over two-thirds of the non-disabled older population report exercising at least once a week.

The Bad News: Less than 25% of Americans of any age engage in regular physical activity at levels recommended by the Surgeon General's Report on Physical Activity and Health. Older adults are especially unlikely to meet the public health goals for sustained activity. For example, less than 10% of older people regularly perform physical activities that enhance and maintain muscular strength and endurance.

More Good News: In the past ten years, several successful intervention programs have increased different types of exercise (strength, endurance, balance and flexibility) without increasing pain or discomfort for middle aged and older Americans. These interventions have increased physical functioning and enhanced quality of life in healthy as well as frail older persons.

Opportunity: The special challenge is to design programs, services and environments that will sustain more physically active lifestyles for all Americans. Exercise interventions have primarily been tested in easy-to-reach, well-educated populations. We need to extend the reach of current interventions by bringing programs to places where older people live and congregate and making environmental changes that will reduce barriers to sustained physical activity across the population as a whole. We also need to increase the delivery of physical activity counseling by primary care clinicians and to test interventions that address barriers to the delivery of preventive counseling in primary care settings.

Obesity/Nutritional Behaviors

The Good News: Under-nutrition is not a major health problem for most Americans. In the past decade, there has been an increase in nutritional information and a greater availability of healthful food choices in supermarkets and restaurants. The percent of calories from fat in the American diet has declined. Additionally, the prevalence of those overweight decreases with advancing age among people aged 55 years and older, with white women least likely to be overweight.

The Bad News: Dietary factors are associated with 4 of the 10 leading causes of death, with obesity strongly linked to conditions such as heart disease, diabetes, and certain cancers. There has been an alarming increase in numbers of overweight Americans, with over 50% of middle-aged and older Americans now characterized as overweight. While many individuals try to lose weight, within five years the majority will regain the weight originally lost. Obesity is especially acute in poor, underserved and minority populations.

More Good News: The average fat and saturated fat consumption has decreased, and average daily consumption of vegetables, fruits and grain products has increased over the past decade, although current public health goals in these areas remain to be realized. Concerted public health programs can change individuals' dietary behavior.

Opportunity: While there have been some improvements, the majority of Americans are still not meeting the nation's dietary guidelines. Strategies for establishing healthy diets must start in childhood and continue throughout adulthood and old age. Programs that link strategies for promoting good dietary habits and increased physical activity need to be developed and tested, especially in health care settings. We also need further testing of clinical interventions for obesity that combine nutritional and physical activity counseling with emerging pharmacotherapeutic agents.

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Smoking

The Good News: The prevalence of smoking rates among adults has declined since the beginning of the twentieth century, although there is a leveling of this trend in recent years. For example, smoking prevalence among men has fallen from 52% in 1965 to 28% in 1994. About 48 million American adults smoke, but approximately 42 million would have smoked without smoking prevention activities. Smoking rates also decline with age with less than 15% of those 65 and older using tobacco products. More than 40 million Americans have succeeded in quitting smoking cigarettes.

The Bad News: In the US alone, tobacco-related disease results in over four hundred thousand deaths annually, representing over 5 million years of potential life lost and direct medical costs of about 50 billion dollars a year. Currently, 50 million Americans are smoking cigarettes. Although overall smoking rates have gone down over the past century, the recent increases in smoking rates among young people, and especially females, are of special concern. While older people are less likely to smoke, those who do, face substantial problems quitting

More Good News: Many effective smoking cessation approaches, policies and resources are available to help those interested in quitting. Also, consensus is emerging on the necessary and key elements of successful programs.

Opportunity: Effective approaches to smoking cessation need to be implemented more broadly. The challenge is to implement effective approaches as widely as possible, especially within primary care settings. One example is the Agency for Healthcare Research and Quality (AHRQ) Smoking Cessation Clinical Practice Guideline. Implementation requires training of health care providers, institutional changes to support the delivery of smoking cessation interventions (e.g., prompts, tracking and follow-up systems in medical records), and reimbursement for counseling and pharmacotherapy. Smoking cessation programs need to take into account ethnic, sex and age-specific differences in smoking behaviors.

Smoking prevention programs and policies aimed at youth are first steps in dissuading a new generation from initiating smoking habits. Such policies include tobacco taxation, school curricula, enforcement of prohibition of sales to minors.

The Role of "Everyday Life" in Health Behavior Initiation and Maintenance

Conceptualizing an Ecological Approach

A number of studies have reported that the characteristics of "everyday life", such as the number and types of a person's daily social contacts and the characteristics of the immediate physical environment, affect the levels of health, function and health behavior. A public health or ecological approach represents a promising strategy to improve the health and well being of populations or communities of older people. This approach makes two assumptions. It assumes that health behavior and health outcomes depend on the interaction between the capacity of the individual and the resources that are available in everyday life, and that this interaction between capacities and resources unfolds over the life course. Individuals are inextricably connected to the biological, physical, social, and historical contexts in which they live.

Ecologically-based programs approach older people as they conduct themselves in their daily lives. Instead of "blaming the victim" or only focusing on individual motivations, this approach examines the person in his or her environment. Such an expanded model is necessary to identify and intervene on the full range of behavioral determinants. These include individual and psychological factors (e.g., knowledge, attitudes, and personality dispositions); interpersonal processes and primary social groups (e.g., relationships between families); institutional and organizational factors (e.g., the health care system), community factors; public policies; and physical environmental factors.

The chances of sustaining healthy lifestyles are improved when social relationships and the physical environment reinforce the individual's healthy behaviors. For example, a person is more likely to be physically active when family members endorse that behavior and the person's physical environment is such that physical activity is viewed as safe, convenient, and inviting. The challenge is to develop programs that address each level: the individual, the social network, and the physical environment.

Identifying Contextual Influences

Context is a multi-dimensional and multi-level concept. It includes the personal, family, small group, neighborhood, community, and society. There are several domains in which context may have a variable interpretation. These are key for understanding the determinants and consequences of different health practices.

Environmental and social contexts: The primary issue is determining how individuals interact with their specific physical and social environments, and how this knowledge can be directed toward potential interventions.

Historical contexts: The developed world is shifting dramatically and populations are aging rapidly. Chronic diseases are now the leading causes of death (with the exception of AIDS). New medical treatments, coupled with successes in public health, are changing expectations about life expectancy and quality of life. Urbanization and technological advances in the 20th century have resulted in a more mechanized workforce and sedentary population. At the same time, there have been positive health changes with regard to smoking and dietary fat. What can we learn from such historical changes?

Market force contexts: Along with societal changes, new market forces also compete with changes in health behavior. They include the availability of inexpensive, high-fat foods, televisions, computers, etc.

Time contexts: With the technological and information revolutions, time and space appear compressed, although more individuals are living longer than ever before. Rapid feedback and quick successes are now part of the public psyche.

Definitional contexts: The public health goal, the "It" we are trying to achieve, needs clarification. Is there a gold standard for physical activity or weight loss that is desirable for all Americans? If not, how does the definition of "It" vary between and among individuals? Should the goal be to move people along a continuum of health behaviors? Who defines successes?

Message/communications contexts: Assuming that the message is known, how should it be conveyed and, perhaps more importantly, how are these messages perceived, processed, and enacted by the recipients? What roles might health care clinicians play in delivering, clarifying and reinforcing health messages?

Successful Intervention Strategies

What Kinds of Behaviors are Recommended for Maintaining Healthy Lifestyles and What are Concrete Steps to Meet These Objectives?

While this report focuses on initiating and maintaining healthy behaviors, it is important to have a clear understanding of what kinds of action or behaviors we are asking people to adopt. The US Department of Health and Human Services sets objectives for the nation in many areas, including attention to physical activity and exercise, nutrition, and tobacco use. The Healthy People 2000 review process coordinated by the Office of Disease Prevention and Health Promotion documents the desired behaviors and evaluates the nation's progress in meeting these goals.

What is Known about Behavior Change Interventions: A synthesis of the scientific literature

Interventions that have been developed and evaluated in the health promotion field typically have aimed to influence a specific level: the personal or interpersonal level, the organizational or institutional level, the health care level, the environmental level, or the policy or legislative level.

The majority of interventions described in the scientific literature to date have been aimed at *personal or interpersonal* (e.g., family or small group) levels of impact. Successful intervention strategies aimed at individuals or small groups typically have included the use of self-regulatory skill training. These include realistic goal setting, self-monitoring of target health behaviors, use of feedback and social support related to the targeted behavior, relapse prevention or preparation training. Often an ongoing level of social support and guidance from a trained staff member has accompanied such skill training. Recent studies have shown that staff counseling and support can be delivered effectively either in person or by telephone, mail, etc.

Interventions have often been tailored to the specific needs of the target group of interest with respect to the program's motivational elements, accessibility, intensity, frequency, and content through the application of social cognitive theory and its derivatives. One example is the concept that human motivation and action are determined by the interplay of cognitive, behavioral and social influences on individual's beliefs about his/her capacities to perform a course of action to attain a desired outcome.

In recent years, greater attention has been placed on fashioning interventions that are sensitive to the motivational readiness of the participant (i.e., early stages of exercise adoption versus maintenance). Brief counseling interventions

that incorporate principles of Motivational Interviewing (e.g., expressing empathy, providing feedback, offering options, supporting self-efficacy, avoiding argument, rolling with resistance) have shown promise in medical settings, as have lay-led group support programs for coping with chronic conditions. Both have successfully increased health behaviors and reduced overall health care costs.

At the *organizational/institutional* level of impact, there is a growing body of evidence to support worksite interventions involving combinations of competition, individual and group goal setting, and the support of management, particularly for behaviors such as physical activity.

The challenge remains to develop ways to incorporate such programs into the worksite milieu, and to attract workers who could most benefit from change. Similarly, schools at the elementary, middle and high school levels have been shown to be effective venues for delivering interventions aimed at smoking prevention and improving diet and physical activity. Here too, we must find ways to disseminate and institutionalize such programs so that their impact lasts beyond the research-funding period.

At the *health care* level of impact, primary care-based interventions are changing the ways that physicians and other health care providers interact with their patients. Primary care physicians are learning how to deliver more effective behavior-change messages to help their patients quit smoking, to increase their physical activity, or change their diets.

Nurse care management interventions have also been successful using proactive behavioral management strategies. These include collaborative, patient-centered goal setting and follow-up support for chronic disease management (especially for heart disease, asthma, and diabetes).

Long-term behavior change at the level of the health care provider as well as that of the patient will require organizational/system level changes such as computerized prompts, training in counseling techniques and resources for patients (e.g., behavioral prescriptions, readable patient educational materials, and access to drug therapy when indicated).

At the *environmental level* of impact, point-of-choice information has been shown to have a positive effect on smoking, nutrition, and physical activity. For example, successful point-of-purchase interventions which encourage people to order health-promoting foods have been conducted in restaurants, cafeterias, and related venues.

Similarly, people respond positively to signs that encourage them to use the staircase instead of the elevator. Researchers have yet to find ways to prolong the effects of such point-of-contact interventions.

At the *policy/legislative* level of impact, strategies that aim to deter cigarette smoking have generally met with resounding success. Such policies include smoke-free building and transportation regulations and statewide increases in cigarette taxes. With respect to diet and physical activity, fewer regulatory policies have been put into place or evaluated. Moreover, reimbursement for professional counseling and pharmacotherapy for nicotine dependence and obesity is needed to reduce barriers to dissemination of interventions in health care settings. Such policy and environmental interventions may hold the key to significant population-wide advances in the dietary and physical activity areas, when combined with approaches aimed at lower levels of impact. Policy changes also provide important opportunities to institute programs at other levels.

Principles of Health Behavior and Behavior Change

There are certain truisms. Americans are generally health conscious. A large number of adults are always trying to stop smoking, start a diet, or become more physically active. Yet sustained change is very difficult. General theories or principles of health behavior adoption and maintenance are emerging to guide the development and implementation of public health programs and policies.

Initiating and maintaining healthy behaviors are best accomplished by taking advantage of the multiple opportunities for change in one's environment. These opportunities can be defined in terms of:

- *Settings* — Interventions can be delivered in a variety of settings where individuals live, work, or play, such as the home, work sites, medical offices, community clubs or senior centers.

- *Situations* — Older adults are in relatively frequent contact with physicians and other health care providers and are often receptive to lifestyle messages if appropriately delivered.
- *Critical periods in people's lives* — The threat of disability, life transitions, the development of a chronic illness or complication, or the physical decline of a loved one can all be "teachable moments".
- *Multiple sources of delivery* — New technologies such as the Internet can make health messages more widespread.
- *Environment/policy* — Interventions can be directed at individuals or populations, as well as through legislation or regulation, as in the case of smoke-free buildings, pedestrian friendly pathways, or mandated nutritional programs.

Favorable/positive cost-benefit ratio is critical to behavior change. People often weigh the potential benefits and side effects of initiating a new behavior. This underscores the importance of interactions between people and their environment. For example, this principle illustrates the importance of considering personal issues in the balance between enjoyment and effort expended. It also leads one to consider interventions that are designed to remove environmental and situational barriers. Failure to recognize offsetting life circumstances, such as competing demands of living with a chronic disease, care-giving responsibilities, or lack of peer/family support can reduce the range and effectiveness of programs.

Basic skills that can be taught can facilitate the adoption and maintenance of healthy behavior. It is important that participants have active participation in goal setting, that they develop confidence in their ability to achieve behavioral goals, and that they acquire problem solving abilities to reduce barriers. Older adults need to be taught how to set realistic goals, to use self-reinforcement strategies, to reduce barriers, and to create positive mind-sets. Intervention participants can be taught how to reflect on achievements and positive feelings associated with behavior change and how to create action for themselves.

Maintaining healthy behavior requires planned follow-up. Despite good intentions, many people relapse into negative behaviors or fail to maintain healthy ones. Programs should build in strategies for addressing probable relapse. Preventing or managing chronic disease requires a shift from thinking about health behavior change as temporary, to thinking about it as lifelong. Effective follow-up need not necessarily involve costly one-on-one contact between interventionists and program participants, but can involve mail, phone or computer contact, or peer support contact.

The goals of healthy behavior change intervention should reflect a partnership between the participant and the interventionist and be stated in concrete terms. The concept of partnership or collaboration places the participant in an active as opposed to a passive role in behavior change. It is designed to create goals that have individual meaning for participants (outcome expectations) and to encourage the perception that goals are attainable (efficacy expectations). People who participate in goal setting are more likely to be motivated to change their behavior. It also can help to avoid "victim blaming," a potential problem in behavior change. Participants who feel their choices are supported by their health care providers are also more motivated to change. Participants should be clear about what behavior changes they want to achieve, when and where they want to work to acchieve the goal, as well as other specific details. For example, an exercise prescription is most effective when it addresses the type, frequency, duration and intensity of physical activity.

The goals of behavior change should be conceptualized as moving targets that are influenced by personal/interpersonal factors, life situations, the environment, and policy. Outcome goals vary, depending on the population (e.g., well versus frail older persons) and the starting point (active vs. sedentary; obese versus overweight; heavy versus more moderate smoker). A key principle is personalizing interventions to meet individual preferences. Interventionists need to take into account participants' capabilities, critical life demands such as work or care-giving responsibilities, and the realities of current physical environments and social policies. Behavioral research suggests that setting smaller but achievable goals that can be updated as the goal is achieved is often advantageous in meeting ultimate health behavior outcomes. Unrealistic goals can lead to disappointment and poor adherence to recommended behavioral changes. Interventions that are responsive to the participants' everyday activities and lifestyles are most likely to succeed.

Interventionists should consider why people change, and in this context evaluate the ability of their interventions to effect change. This principle leads one to consider the important issue of participants' readiness to change and individual, social and environmental barriers to change. A multilevel approach to understanding and modifying behavioral change determinants can enhance their effectiveness. Moreover, it underscores the importance of evaluating the effectiveness of current methods being used to change behavior in individual and/or group settings. Intervention strategies should be based on presumed pathways of action. There is a voluminous literature on two key mediators—efficacy beliefs (i.e., the idea that people can perform certain tasks successfully) and outcome expectancies (i.e., the idea that particular behaviors will be related to desired outcomes). Expensive strategies are not always the most effective. Merely providing information, such as in mass media campaigns, is often ineffective unless the intervention is built on behavior change principles. Television-based messages can be effective in changing attitudes and norms connected to lifestyle behaviors if the message is powerful and if it provides meaningful and clear information and expectations about that behavior.

Models of Successful Change

Behavioral change interventions can increase the adoption of healthier lifestyles, resulting in improved health outcomes and lower health care costs. What do successful interventions look like? What kinds of strategies have been employed? What populations are targeted? And what kinds of outcomes achieved?

This report describes three model interventions:

Using Exercise Interventions to Prevent Further Disability in Older Adults

A randomized trial by W.H. Ettinger and his colleagues examined the effects of exercise therapy on knee pain, functional limitations, and disability in older adults who had knee osteoarthritis. This study involved the random assignment of 439 patients to one of three treatment conditions: a health education control group, aerobic exercise, or resistance exercise. The exercise therapy involved shaping the behavior of participants' activity to a 3-month goal of 40 minutes of exercise performed 3 times each week. The exercise sessions were conducted in a structured center-based program for 3 months followed by home-based training for another 15 months. Trained physical activity therapists used phone counseling to manage home-based exercise. This counseling was tailored to each patient's needs and employed strategies such as problem-solving, goal-setting, self-monitoring, support, and reinforcement. Although both exercise conditions were successful when compared to the health education control group, participants in the aerobic exercise group experienced the greatest reductions in knee pain and the most improvement on tests of physical performance and self-reported disability.

In other studies published from this trial, W.J. Rejeski and his colleagues reported on some very intriguing dose-response effects and on mediators of change in function. With respect to dose-response effects, analyses revealed that patients in the aerobic exercise group who benefited the most from treatment were in the middle third of compliance for duration of exercise. In fact, those patients in the highest third for compliance had pain ratings and a functional status at 18 months that did not differ from the control group!

These findings underscore the need for patients and health care providers to collaborate in establishing goals for treatment. Furthermore, they speak to the need for accepting modest levels of achievement as indicators of success.

In a study on mediation, Rejeski et al. examined the role of self-efficacy and pain in explaining the effect that exercise therapy had on improvement in function. Interestingly, they found that the effect of exercise therapy on change in physical performance scores was due to a reduction in pain and the enhancement of self-efficacy beliefs.

These data suggest that future studies are needed to determine whether combining exercise therapy with coping skills training could enhance the independent effect that exercise therapy has on health outcomes in diseased populations.

Improving Dietary Practices in Populations with Chronic Illnesses Through Self-Management

A randomized study by R.E. Glasgow and colleagues combined patient-centered self management with interactive computer technology to enhance dietary self-management among 206 adult patients, average age 62 years, having type 2 diabetes.

This study integrated behavioral intervention into the clinic flow of a primary care office setting. The study focused on delivering a brief, yet effective, intervention that would be feasible and appeal to a variety of patients.

The study began by contacting all adult diabetes patients who had scheduled a visit with one of two internists. Sixty-one percent of eligible patients agreed to participate in the study.

Of importance, there were no differences between participants and non-participants in demographic or medical characteristics collected.

The intervention package involved the following sequence: a 15-minute touch-screen computer assessment which helped subjects identify dietary goals and barriers to accomplishing the goals; immediate scoring and printing of two tailored feedback/goal print-outs summarizing the information–one for the patient and one for the physician; a 20-second motivational message from the physician emphasizing the importance of the patient's goal; a 15-20 minute meeting with a health educator to review the goal and collaboratively develop problem-solving strategies to overcome barriers; and finally, two brief follow-up phone calls from the health educator to check on progress. This sequence was repeated at a regular 3-month follow-up visit.

Compared to a stringent, randomized control condition that received the same touch-screen computer assessment (but no tailored feedback or counseling), and physician encouragement, the intervention produced significantly greater improvements on a variety of dietary behavior measures (total and saturated fat intake, changes in dietary practices) as well as serum cholesterol levels. More importantly, these results were maintained at essentially the same level (e.g., adjusted difference of 15 mg/dl in serum cholesterol and 2.2% of calories from fat) at a 12-month follow-up, and the intervention was found to be cost effective: An average, annual incremental cost over usual care of $115-$139 per patient and $8.40 per unit reduction in serum cholesterol level.

Model Smoking Cessation Program for Older Adults

A randomized controlled study, conducted by G.D. Morgan and colleagues, tested the effectiveness of an office-based smoking cessation program tailored to smokers aged 50-74. Thirty-nine primary care community-based medical practices were assigned to either an experimental condition or usual care. Physicians and other clinical staff within practices in both settings received a 45-60 minute on-site training session that oriented them to the goals and objectives of the study. Experimental practices also received multiple academic detailing visits from research staff to provide clinicians with training in brief smoking cessation counseling using the National Cancer Institute's 4 A's Model (e.g., Ask, Advise, Assist, and Arrange) and to assist clinicians and staff in adopting practice-based tools to assess and monitor smoking status and prompt clinicians to deliver smoking cessation interventions.

Patients in experimental practices also were given access to *Clear Horizons*, a self-help smoking cessation manual that was developed specifically to meet the needs of older smokers. Smokers from intervention practices who were enrolled in the study received a follow-up letter within 1 week and a telephone counseling call within 2-4 weeks of their office visit. Nicotine replacement therapy in the form of nicotine transdermal patches was also made available to clinicians and patients in experimental and usual care conditions.

The investigators analyzed the effectiveness of the intervention among 659 subjects. Self-reported smoking cessation rates at 6-month follow-up were 15.4% for the experimental group versus 8.2% for subjects in the usual care group ($P < 0.005$). Eighty-six percent of subjects in the experimental group reported receiving a recommendation to stop smoking from their physician and 96% received the *Clear Horizons* guide. Subject characteristics related to 6-month abstinence included the number of previous attempts to quit, quitting for 24 hours in the past year, desire to quit, confidence in quitting,

perceived health benefits, and lower levels of nicotine dependence.

This study demonstrated that smoking cessation among older adults can be significantly increased in primary care settings by a practice-based intervention that provides smoking cessation counseling training to physicians and clinical staff, self-help materials tailored to meet the needs of older adults, and practice-based systems to prompt and support clinicians to regularly deliver smoking cessation counseling and follow-up.

This finding is consistent with the results of smoking cessation interventions found to be effective in the general population of smokers.

The Complexities of Maintaining Health Behavior Change Over a Lifetime

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Variability in Health Behaviors, Interventions and Populations

Aging and human development is characterized by variability in individual interests, capacities, and responses to motivational messages that encourage physical activity, dietary change, or other lifestyle modifications. Not only does variability in human beings necessitate that information be tailored; the very existence of individual differences offers powerful evidence that age is not invariant, with little or no opportunity for change. There is always some benefit to be gained from any of these lifestyle modifications, as long as it is a change that occurs with regularity.

Messages that are targeted to reach particular communities are more effective than "boilerplate" motivational messages. People of all ages and in all socioeconomic categories can benefit from healthier lifestyles and behavior modification if the message is personalized. The emergence of detailed, personalized programs for health promotion and disease prevention is significant. Computers, touch-screen kiosks in medical care centers, the Internet, and automated voice messages, have enabled health care professionals to target specific populations.

These advances are impressive, but much still needs to be learned about how to personalize programs more effectively, how to determine the importance of a variety of factors, such as cultural beliefs, preferred learning style, body weight, or functioning level, for specific sub-groups.

Interventionists need to specify and carefully weigh what is being tailored: the source of an intervention, the recruitment message or the way it is framed, the approach or content of the intervention, or the constituency of the group that receives the intervention. The level of hetergeneity likely will determine how important tailoring is and the individual characteristics on which to tailor, such as cultural beliefs, preferred learning style, body weight/BMI, or functioning level.

Although we don't know as much about less educated, underserved populations, research suggests that the same behavioral strategies (e.g., structuring early expectations, ongoing monitoring of behavior, provision of meaningful feedback, planning for relapse, and ongoing social support) are also effective in promoting behavioral change with regard to smoking, dietary change, and physical activity in these populations.

Interventions that target disadvantaged groups, as well as other segments, are generally more effective when participants are actively involved. Interventions need to be culturally relevant if they are to reach a variety of ethnic or racial groups. In addition to attitudes and values, financial and access barriers have to be addressed for more disadvantaged groups.

There are several potential downsides to tailoring, including: the cost and impracticality of tailoring on a large number of variables; some participants may not have adequate experience to tailor or choose preferred interventions; and the possibility of contributing to isolation, polarization, and separation of different subgroups.

Motivating factors also need to be identified at the community or larger group/organizational level. For example, the concept of social capital—presence of family and community-level resources—goes beyond an examination of individual resources. Moreover, the degree to which different service organizations or features of the actual physical environment are connected is also important for assessing connections to a participant's community. Settings such as states, regions or nations can also act as barriers to change. However, they can also be gateways for diffusion to family, other community members, or organizations.

Motivating Long-term Adherence and Interconnections Across Behavioral Domains

In all of our efforts to stimulate middle-aged or older adults to engage in regular and meaningful lifestyle modifications, it is clear that we are far more successful in gaining initial levels of interest and participation than we are in sustaining interest and participation over the longer term. Far more research has been devoted to the study of "early successes" than to "long-term maintenance" of these behaviors and lifestyle changes. Not only has there been more research on early success, but most programs or interventions with these goals are able to register these early successes among their participants, and most report high levels of satisfaction as well.

Yet, there are variations in the number of participants who are exposed to all segments of these intervention programs. Researchers report that follow-up monitoring of subject behaviors and maintenance of lifestyle changes are difficult to carry out. These studies are difficult to finance, and it is difficult to maintain subject contact over an extended period of time so that follow-up measures can take place.

Studies of the early phases of lifestyle change among middle aged and older adults may help us unravel the perplexing questions of why changes and levels of participation are so difficult to sustain over the longer term. First, many people simply are not aware of the health benefits of moderate, but regular long-term lifestyle change. Among people in some age categories, and in some populations, there is a lack of publicly-accessible information about the potential for life-long health behavioral change. There needs to be more appreciation for the adage: "It's never too late to start, and it's always too early to quit!"

The labeling and packaging of lifestyle modification programs may also affect the way in which these programs are perceived. If a program offers to help its participants "increase physical activity", it may be seen as less negative than if its stated goal is to help participants "overcome sedentary lifestyle patterns." It is critical that these programs emphasize what participants can do to adopt positive lifestyles, and that they build in strategies to help maintain life-long adherence.

There is controversy about the extent to which people respond to more than one goal or aspect of lifestyle change. Despite program planners' beliefs that programs which address one aspect of an individual's lifestyle may have an effect on others, it is still unclear whether or not "behavioral synergy" exists. Currently, a national research effort is underway at the National Institutes of Health to examine the best ways that multiple behavioral change can be introduced and reinforced.

Other suggestive conclusions from our previous studies of the short-term effects of lifestyle interventions have implications for how we might increase the prospects for longer-term maintenance of healthy habits. For example, persons who enter intervention programs with a generally "positive attitude" — a feeling that this is something they enjoy and want to do, with expectations of health benefit, and an attitude of self-efficacy — are more likely to demonstrate early success in the achievement of program and personal goals. Experiencing optimal nutrition, physical activity, sleep and relaxation can be a powerful motivator for long-term adherence.

A profile is emerging of factors which we can associate with long-term success in achieving and sustaining recommended health-relevant lifestyle changes. Persons with strong social support, who are motivated and open-minded in their approach to lifestyle modification, who believe that they can make these changes through their own personal effort, and whose environmental situations make these changes feasible are most likely to be successful.

Furthermore, a central feature of such programs should be the message that benefits accrue from the regularity with which changes occur. Experiences with short-term effects of lifestyle intervention programs suggest that longer-term maintenance of achieved goals should allow for more modest, less-than-optimal shorter term achievement goals, with both participants and program sponsors accepting these more modest levels of achievement as indicators of success.

This observation is not intended to negate the importance of engaging in certain levels and intensities of physical activity or exercise, weight loss or smoking cessation to achieve specific health outcomes. At the same time that these programs offer a sense of the benefits of moderate effort required for longer-term gain, it is important to prepare participants for possible relapse and steps that might offset these setbacks. The strategies that successful participants use to sustain health behavior changes should be shared with participants who have difficulties adhering to a program.

Rather than defining relapse as "failure," programs should include instruction and guidance in relapse prevention or preparation as a normal part of the intervention. Relapse should be treated as part of the realistic understanding of the way in which these changes will span the whole of one's life. It is important to stress that it is the general direction of lifestyle modification that is important, not the speed with which these changes may occur.

Research Gaps and Future Research Directions

As with any aspect of complex behavioral change, there are theoretical and empirical gaps in our understanding that should be addressed through subsequent research.

Tailoring by Risk, Behavior and Developmental Stage

A key issue that deserves further research is how to target interventions so they reach broader segments of the population and, in particular, those at highest risk. This category includes the morbidly obese, or sedentary, those with serious chronic diseases (hypertension, diabetes, arthritis, etc.), or with mental health problems (social isolates or those with depression.)

In contrast to smoking and diet, relatively little systematic work has gone into understanding the most effective way to frame messages that promote the adoption and maintenance of physical activities. This is of particular concern with respect to people who are sedentary. Scientifically testing the impact of different

types of messages (positive, fear-inducing, etc.) will facilitate a better understanding of how best to frame messages that promote individual as well as population-wide changes in physical activity behavior.

In addition to understanding the environmental, social, and cultural contexts of health behavior, we need a better understanding of the developmental context in which health behaviors are formed and enacted throughout life. For instance, investigators might examine how prevalent developmental milestones influence these health behaviors. Milestones include events such as transitions into and out of the workforce, marriage; parenting and other care giving duties. This information could help to identify potential 'windows of opportunity' during which to intervene.

Targeting Multiple Behaviors

We need better understanding of how physical activity, smoking and dietary behaviors may be addressed in intervention programs across the life-course, either alone or in combination. For example, we do not know whether it is possible or even effective to address more than one health factor at a time. This has implications for tailoring interventions of personal importance to participants.

We do not know whether too many concurrent behavior changes are expected in many health and lifestyle intervention programs. There is a lot of interest in giving participants the opportunity for "cross-training" in more than one activity. The rationale is that it may offset the likely frustrations of slow initial progress, and increase general interest in active behavioral change. We are not sure how these programs should stress strict adherence to guidelines in terms of the likely impact on important health outcomes.

Although dietary and physical activity behaviors share important physiological synergy and likely some behavioral synergy as well, these two health behaviors continue to be studied primarily in isolation from one another. Furthermore, professionals who deliver interventions (e.g., dieticians) are typically trained in only one or two health behaviors and have been reported at times to be reluctant to deliver information or strategies related to the other health behavior.

Promoting Clinical and Health System Interventions

The major health problems of the twenty-first century will be associated with chronic conditions, although there has been a recent resurgence of acute or infectious illnesses. However, the health care systems and models are designed to respond to acute crises — to treat symptoms and respond to specific problems — rather than to help patients manage chronic illness over a lifetime.

In the past five years, several randomized trials have demonstrated the benefits of redesigned health care system approaches to both the prevention and management of chronic illness. The majority of these interventions have focused on planned, population-based approaches that rely on clinical information systems, collaborative goal setting with patients, intervention coordination by non-physician staff (often nurse care managers) and follow-up support. We must find ways to better understand the health care system factors related to adoption and successful implementation of such innovations, so that they are more broadly adopted.

Major challenges before us involve reshaping the health care system to center the diagnosis and treatment plan around the needs and preferences of the patient rather than the more typical provider-dominant system. The conceptualization of health education must be changed from

the one-time, didactic inoculation patients receive shortly after diagnosis that is unrelated to ongoing care, to an ongoing and collaborative problem-solving process with patients and families that is an integrated part of primary care.

Over the past decade, health care has become more evidence-based. A variety of evidence-based guidelines, performance indicators, and flow sheets have been developed, but they are generally not followed and seldom include behavioral or patient-focused activities. Changing the behavior of health care providers has proven to be as challenging as changing the behavior of individuals.

Goals for the future include finding ways to successfully disseminate and implement these guidelines, with allocation of limited resources where they are most needed. The success of the human genome project and the advent of genetic and other biomarkers raise a plethora of complex ethical, logistic and risk communication issues that we are only beginning to understand. The communication and prioritization of intervention recommendations for both providers and patients will become much more central over the next decade.

The quality and content of clinician-delivered counseling to enhance patient behavior change is an important area for future research efforts. Brief counseling interventions that incorporate principles of motivational interviewing and patient-centered approaches have shown promise in medical settings. Recent population-based studies suggest that patient adherence is enhanced when the patient believes the physician knows him/her as an individual, and when the patient expresses high levels of trust in the physician. Subsequent research in this area should focus on strategies to identify the preferred decision-making style of patients and on testing strategies that match clinician counseling style to patient preferences.

Enhancing the Social and Physical Environment

Although the social environment has been consistently identified as an important correlate or predictor of change in both physical activity and diet, we know relatively little about the effects of different aspects of the social environment on behavior change in different subgroups. In addition, questions remain concerning the mechanisms through which the social environment exerts its effects on behavior change in these health areas.

In general, lower socio-economic groups remain at greatest risk for smoking, inactivity and poor dietary practices across different racial/ethnic groups. We need a greater understanding of the multiple ways in which socioeconomic status has an impact on health behaviors, and how social status interacts with ethnic values and beliefs to influence health attitudes and behaviors.

Despite a growing body of research indicating that social and physical environmental factors affect levels of health, well-being, and behavior, there are relatively few environmentally-based intervention programs. There are several reasons for the absence of such programs. First, it is often difficult to conceptualize and measure objective characteristics of the physical environment (e.g., housing and neighborhood features), especially change. Second, it is difficult to determine the strategies individuals use to adapt to features of the physical environment. Third, studies of living arrangements and social networks usually involve surveys of individuals who are asked to report the number and types of their social relationships. The people involved in these networks are typically not studied directly. There have been few opportunities to study social relationships, for example, the social exchanges between spouses, and the extent to which those relationships are affected by

recommended health behavior. Finally, although it is often feasible to randomize individuals in experimental/evaluation studies, it is more challenging to randomize groups and communities.

Nonetheless, a systematic assessment of current environmental research with an eye toward the translation of that research to public health and individually-based programs is needed. This involves a review of evaluation studies of current programs to identify areas for needed improvement and to determine which current programs should be implemented more broadly. This is an especially fruitful time to initiate a new generation of studies in this area. In addition to the recognized need for research, there are new sets of analytic and statistical techniques that integrate environmental variables into behavioral research.

It is also important to identify channels through which health behavior interventions could be consistently delivered throughout an individual's life. Although systematic training of primary care providers in the delivery of brief behavioral interventions for smoking, diet, and physical activity has shown promise, the programs have often been limited to medical residents, general internists, and family practice physicians. Notably absent have been interventions aimed at other providers who play major roles in people's lives (e.g., pediatricians, obstetrician-gynecologists, geriatricians, dentists, pharmacists). The support of health care clinicians in sustaining and maintaining change has not been adequately addressed in intervention design and implementation.

Fostering Research Collaborations

In-depth national data are often lacking on the multi-level determinants and consequences of different health practices and lifestyles. For example, research is needed to understand more clearly the reasons why many older people limit or avoid physical activity, while others remain active into their later years. That research, in turn, should serve as the basis for the development of a new generation of interventions to promote and enhance physical activity in older populations.

Core items should be developed. They could be assessed in major national and community-wide health surveys, with representation from all age, income and racial/ethnic groups. Similarly, information on health behaviors and behavioral change processes can be incorporated into smaller clinical studies to examine the interaction of genetic, biological, behavioral and environmental influences.

Efforts are needed to establish collaborations within and across disciplines. Fields of relevance include clinical and biological sciences, gerontology, epidemiology, health services research, sociology, anthropology, economics, health and environmental psychology, exercise physiology and nutrition sciences, urban geography, traffic engineering, architecture, and city planning. Additionally, the public health and academic community has traditionally remained relatively isolated from private sector activities, which aims to collect empirical information on the very health behaviors that we are most interested in understanding (e.g., marketing surveys undertaken by the food industry) or practitioners actually conducting health promotion interventions (e.g., fitness centers or health resorts.)

People who attend fitness centers or spas may in turn be encouraged to promote healthy lifestyles in their communities (e.g., ensuring that schools in their communities have physical education programs and provide healthy meals.) By sharing information, perspectives, and ideas among such groups, the behavioral database may be advanced.

Testing Innovative Approaches to Behavioral Change Interventions: The Next Generation

Several promising interventions are now ready for further testing or modification to broader audiences. Research and practitioners need to:

- Design and test exercise, smoking or diet interventions that include social contact and social support. One example is a "buddy system," which may be especially appropriate for older women who live alone.
- Examine the effectiveness of family-based intergenerational health promotion programs (e.g., grandparents and grandchildren walking together.)
- Promote lay-led group support programs for coping with chronic disease, and expanding the successful arthritis self-management and diabetes programs.
- Encourage volunteerism as a potential resource for leader-based health promotion efforts. The training and utilization of group leaders appears to have supplemental beneficial effects on behavioral change for those particular individuals.
- Introduce different stepped-care approaches as a way of testing the effectiveness of various behavioral tailoring strategies, such as starting with a minimal set of behaviors needed to affect desired change and increasing them as initial goals are accomplished.
- Establish exercise interventions that are based on a modest modification of everyday activities, e.g., balance exercises while standing in line and stretching exercises while watching television ("What to do when you are not doing anything.")
- Establish exercise interventions that take into account the resources that are available in the person's neighborhood and community, such as walking paths, gymnasiums, "mall walking" programs.
- Form alliances with agencies that set and enforce architectural, building, and safety standards affecting the environments (e.g., development and transmission of age-appropriate criteria for the timing of pedestrian crossing lights.)
- Design "hierarchical interventions" that are directed to both individuals and to the social and physical environments. It will be very important to determine to what extent the overall effectiveness of an individually-based intervention (e.g., information and training in particular types of exercise regimens) is enhanced by including an environmental component (e.g., access to a safe and convenient walking path or access to a local high school gymnasium.)
- Train all physicians, nurses, dieticians, occupational and physical therapists in patient-centered motivational and behavioral change counseling strategies to enhance intervention delivery.
- Design interventions that combine brief messages from primary care physicians with more intensive motivational and behavioral counseling interventions from allied health professionals or tailored educational interventions delivered by computer-based expert systems.
- Include evidence–based behavior change interventions in clinical guidelines, along with implementation programs and incentives, including reimbursement for delivery of behavioral counseling and effective pharmacotherapy, to support the use of these guidelines.
- Address clusters of health behaviors by combining creative media-based messages with targeted behavioral and environmental interventions.
- Standardize packaged interventions via manuals and especially computer- based interventions delivered via web-TV, touch-screen kiosks and other modalities that do not require time on the part of overworked health care providers.

- Develop culturally sensitive interventions in multiple languages, especially Spanish.
- Employ community role models and charismatic leaders to promote health behavior change messages.

Translation, Dissemination and Networking

Whatever our success in achieving either short or longer-term lifestyle modifications, most of the documented success in such intervention programs has been limited to rather small, defined populations in particular communities, worksites, schools, neighborhood organizations, senior centers, health centers or clinics. The next challenge is to spread the benefits of such programs to wider communities of potential participants. This is a priority for national prevention policy.

Effective home, and in some cases, worksite and community-based, interventions have been developed which can substantially enhance the reach and maintenance of lifestyle behavior change programs. The success of practical behavioral interventions conducted in participants' social environment significantly increases potential public health impact.

Program evaluation should include an assessment of reach (participation rate and representativeness of participants), effectiveness under non-research conditions, adoption (percent and representativeness of settings willing to attempt an innovation), implementation or intervention integrity under field conditions, and finally, maintenance of both individual behavior change and organizational-level delivery of services.

We need to better understand the variability in outcomes across both individuals and settings on multiple outcome dimensions (e.g. reach and participation, program replication and diffusion, short vs. long-term effects) to develop interventions that can have broad impact on non-research settings and at the population or public health level. A broad range should be considered—behavioral outcomes, health and functional outcomes, quality-of-life outcomes, and health care use and cost outcomes. The ultimate outcome of interest is clinically meaningful results that produce differences in everyday life functioning.

Outcomes are likely to be temporal. A variety of shorter-term individual-level outcomes that are important can be identified, including reach and participation rates, participant-defined goal attainment, participant satisfaction, and economic outcomes such as cost-effectiveness. At the program or setting level, outcomes in need of increased attention include health care provider implementation of intervention protocols, spread or generalization of program impacts, and effects on the 'culture' of an organization, region or even nation. Just as individuals can be assessed on their readiness to change, organizations can be evaluated on their readiness for action.

Effective dissemination efforts will involve more than "marketing." They will require achieving scientific consensus on the minimum elements of an effective intervention program. As indicated in this report, there is a growing consensus on processes of behavior change and an increase in the number of evidence-based studies demonstrating the efficacy of behavioral and environmental intervention strategies for initiating recommended behavioral change in the realms of smoking, physical activity and nutrition. It is also critical that there be a societal consensus on the value of the proposed intervention strategy and stated intervention goals.

For example, any attempt to encourage increased levels of physical activity as part of everyday behavior at all adult ages, including efforts to

introduce this type of activity at the workplace, in home and community settings, will require both national organizations with a concern for prevention policy development, and the financial resources to communicate relevant public health messages about both the benefits of increased physical activity and suggestions for how activity may be increased in the context of everyday social behavior.

Slogans that immediately communicate the essential message, and benchmark standards for adequate levels of activity, should become commonplace. For example, a slogan like "10,000 steps to better health!" might come to signify the number of steps a person should walk in a single day in order to maintain aerobic fitness. Of course it matters how these steps are taken, and over what period of time, but the first phase of national awareness of the current extent of sedentary lifestyle (without even mentioning the often pejorative term "sedentary") is to enable people of all ages to ascertain the extent to which they currently meet these minimal expectations for physical activity in a single day, or average per day over a week.

Inexpensive pedometers which can easily take these type of measurements, are now available. They are useful for educational and monitoring purposes. Once it becomes part of the social fabric of a community and people become accustomed to hearing about the number of steps their neighbors are logging in a single day, they will likely be motivated to expend "additional effort." In this way, physical activity may increase in a community setting the same way that designating a person in any group to drive, and therefore consume less alcohol, assures the safety of others.

For any national effort toward lifestyle modification to be successful, especially one that involves structural changes in the way people live and work, efforts must be made to prepare local communities. This would help to ensure the availability of opportunities for individuals to make decisions regarding personal behavior changes, and opportunities for non-judgmental feedback and reinforcement while these changes are being attempted.

The networking arrangements that might facilitate such national efforts would include governmental agencies such as the Centers for Disease Control and Prevention (CDC), the National Institute on Aging (NIA/NIH), the Surgeon General of the U.S. Public Health Service, and the Office of Disease Prevention and Health Promotion of the Office of the Assistant Secretary for Health, US Department of Health and Human Services, as well as advisory groups such as the President's Council on Physical Fitness and Sport, or the Parks Council. Schools and universities can also serve as important settings for promoting a healthier lifestyle message for younger populations and their families.

Private and voluntary sector organizations (such as the American Association for Retired Persons, American Heart Association, the AFL/CIO, the American Cancer Society, the American Diabetes Association) might share an interest in the health-protective impact of regular patterns of physical activity. The nation's private philanthropies are in a unique position to support the national launch of this campaign, as well as the dissemination of key materials explaining the health benefits of regular physical activity to target populations in key communities nationwide. Similarly, the media and entertainment industry can play a role in promoting healthy lifestyles for all Americans.

Action Steps

We have identified many of the pathways by which the health of Americans are directly linked

to lifestyle patterns. Lifestyle choices are influenced by legislative, social, economic and physical environments — many of which are changeable. The urgent challenge that lies before us is the mobilization of public and private sector resources to improve the population health of this country through evidence-based programmatic strategies that will reach large segments of society.

National Healthy Lifestyle Campaigns

The beginning of a new millennium presents a unique opportunity to organize and initiate national campaigns for healthy lifestyles, beginning with the big three: physical activity, nutrition and smoking.

Key Elements:

- Attainable health-enhancing goals
- Scientific evidence-based programming
- Clear, appealing messages
- Charismatic leadership and role models
- A competitive component to enhance involvement
- Cultural relevance
- Federal, state and local support
- Partnerships and coalitions between private and public sectors
- Mobilization of volunteer corps
- Media coverage
- Mass participation

Strategic Action Proposals

National Walking Program – Aimed at increasing the level of physical activity of the population, a nationwide walking program will organize safe and accessible walking paths in streets, parks, schools, worksites and malls for walking groups of all ages and abilities. The program would be sponsored by a partnership of private corporations and state and municipal grants and organized at the community level by schools, workplaces, non-government and government organizations, and the media industry.

National Healthy City Competition – Cities and communities of similar size will be paired (grouped) for a competition to improve indicators of healthy lifestyles in the areas of physical activity, nutrition and smoking. Health statistics will be assessed by the NIH or other governmental bodies to monitor change over the length of the program (e.g. 2001 - 2010). Indicators of healthy lifestyles could also be included in the criteria for the selection of "All-American Cities."

National Media Lifestyle Campaign – Initiation of a multi-pronged multimedia (e.g., television, radio, Internet) advertising campaign aimed at providing key information and methods pertaining to short-term and long-term lifestyle modification in the areas of physical activity, nutrition and smoking. Included in the message will be attainable lifestyle goals for individuals, available resources, and a motivational component reinforcing the importance of lifestyle enhancement and maintenance. One key print resource that could assist in the development of the message is *Exercise: A Guide from the National Institute on Aging*. Demonstrating the importance of a multimedia approach, this is matched with a 48-minute video. It illustrates how to start and stick with a safe, effective exercise program that includes aerobic, stretching, balance, and strength-training routines.

National Physical Education Standards – Mandatory physical education standards, including health education that covers health behaviors, could be developed and implemented into school curricula nationally and at the state level. For example, all students must have at least two one-hour classes of physical activity per week that include

aerobic and strength training components and at least one hour of health education.

National Program for Senior Citizens – Development of a national community-based program to incorporate healthy behavior messages and health promotion activities, with special attention to senior centers and retirement centers. These programs can be initiated through federally-funded area agencies on aging, which are located in each of the states and which provide a variety of services for older people.

Network Centers for Healthy Lifestyles

In support of all of the recommendations in this report, there is a need for the development of several technical resource centers — Network Centers for Healthy Lifestyles. These centers could be formed within schools of public health or centers on aging with direct links to local and state services, key government institutes (e.g., NIH and CDC, etc.), existing health promotion and disease prevention centers, and private foundations aimed at improving and sustaining healthy lifestyles.

Functioning as a clearinghouse and training institute, as well as a proactive networking service, the centers would facilitate the capacity for coalitions to be forged between public and private organizations through the collection, synthesis, evaluation, and dissemination of important research-based evidence coupled with details of successful community and international experiences.

The centers would also provide teaching and mentoring programs for the development of grant-writing skills targeting individuals, groups, and organizations with program development experience or potential but without the professional expertise to design and evaluate programmatic efforts.

International Center for the Initiation and Maintenance of Healthy Lifestyles

The action steps outlined in this report need to be organized and sustained through a central organization. Either an established center with this mandate or one newly formed would play a leading role in the mounting of the strategic action plan nationally and would act as the liaison with the World Health Organization (WHO) as well as sister organizations in other countries and regions (e.g., Pan American Health Organization). One role would be the organization of an international conference to help raise the public consciousness of these important population health issues and campaigns.

International Conference on the Initiation and Maintenance of Healthy Lifestyles

An international conference developed in conjunction with the WHO would provide a timely opportunity for the exchange of knowledge and ideas on the topic of "Initiation and Maintenance of Healthy Lifestyles Across the Life-Course." Experts from both research and practice environments will be brought together to exchange knowledge and to promote international strategic planning and action plans.

Bolstering the National Research Infrastructure

Current research efforts are adding to our understanding of the determinants of behavioral change, the most effective interventions for promoting healthy lifestyles, and strategies for translating and generalizing research to the broad American population, especially those at greatest need. Yet, long-term support (e.g., ten years or more) is critically needed to meet the nation's health promotion objectives. Long-term studies are needed to document natural

health behavior changes and to evaluate the effect of targeted interventions and dissemination plans. Of special interest are multi-site initiatives that test best intervention strategies across a wide spectrum of ages, target behaviors and conditions.

Support is also required to ensure that health-promotion questions get incorporated into major national surveys as well as smaller community-based studies addressing the full range of biomedical, behavioral, social and environmental influences on the health and functioning of Americans throughout their life-course. The nation can benefit from three to five Research Centers of Excellence in Health Promotion and Aging. These Centers would provide core support and research dollars to bring the best social and behavioral scientists together with clinicians, community administrators and planners, and policy makers to conduct basic and applied research aimed at promoting healthy behaviors and lifestyles in later life.

Changing Medical and Health Care Practices

In recognition of the powerful influence that physicians, nurses, and other health care providers have on influencing the health behaviors and lifestyle choices of their patients, it is critical that medical and health professional curricula and continuing education activities include information on health behavior change and skill training to help students and clinicians utilize effective motivational and patient-centered behavioral counseling techniques. System infrastructure changes in the health care setting will be needed to encourage patients, their families, and health care providers to engage in preventive interventions that address behavior change. This will be accomplished through cueing doctors to ask about health practices and providing third party reimbursement for health promotion counseling in health care settings.

Practical Strategies for a Healthier Lifestyle Through Autonomy and Self Management

- Establish a goal and make a contract with yourself. The three vital areas to target are nutrition, tobacco cessation and physical exercise.
- Personalize your program to address special needs or health risks, such as diabetes, high blood pressure, high cholesterol.
- Find convenient and inexpensive ways to achieve your goals.
- Self-monitor your efforts. If your goal is weight loss, write down exactly what you eat. If your goal is to become more physically fit, wear an electronic-based pedometer to clock the number of steps you take in a given day, whether you walk, jog or run.
- Build healthy habits and activities around your schedule. Establish routines that are environment-friendly, at the workplace, school and home.
- Find a role model to emulate in adopting a healthier lifestyle.
- Establish a peer-support system. Mutual support encourages compliance, whether it be a partner, a club or family members.
- Establish a professional-support system with a physician or fitness trainer who can offer guidance and support.

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The International Longevity Center – USA (ILC-USA) is a not-for-profit, non-partisan research, education and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways and highlight older people's productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium, which includes centers in the U.S., Japan, Great Britain, France and the Dominican Republic. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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